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THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office 09/937667

February 04, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/126,521***
FILING DATE: ***March 26, 1999***

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
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By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

A/PROV

Please type a plus sign (+) inside → [+]

Docket Number: 98,710

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Ralph	Scannell	Hopkinton, Massachusetts

☒ *Additional inventors are being named on page 2 attached hereto*

TITLE OF THE INVENTION (280 characters max)

COMPOUNDS AND METHODS FOR TREATMENT OF ASTHMA, ALLERGY AND INFLAMMATORY DISORDERS

CORRESPONDENCE ADDRESS

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☐ Customer Number [ ] → *Place Customer Number Bar Code Label here*

OR

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification — *Number of Pages* 48

☒ Drawing(s) — *Number of Sheets* 10

☒ Other (specify) — Title Page (2 sheets)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☒ A check or money order is enclosed to cover the filing fees — FILING FEE AMOUNT: $150.00

☐ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: [ ]

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ DATE March 26, 1999

TYPED or PRINTED NAME Michael S. Greenfield REGISTRATION NO. *(if appropriate)* 37,142

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USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231

P18LARGE/REV04

PROVISIONAL APPLICATION FOR PATENT COVER SHEET (Large Entity)

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Marie-Agnes	Lassoie	Braine-le-Chateau, Belgium
Michelle	Young	Belmont, Massachusetts
Xiong	Cai	Belmont, Massachusetts
Sajjat	Hussoin	Lexington, Massachusetts
Gurmit	Grewal	Natick, Massachusetts
Timothy	Lewis	Framingham, Massachusetts

Certificate of Mailing by Express Mail

I certify that this provisional patent application cover sheet, provisional patent application and fee is being deposited on 3/26/99 with the U.S. Postal Service as "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Erik VARELA

Typed or Printed Name of Person Mailing Correspondence

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Attorney Docket No. 98,710)

Title: **Compounds And Methods For Treatment Of Asthma, Allergy And Inflammatory Disorders**

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COMPOUNDS AND METHODS FOR TREATMENT OF ASTHMA, ALLERGY AND INFLAMMATORY DISORDERS

BACKGROUND OF THE INVENTION

Field Of The Invention

The invention relates to the field of 1,4 substituted piperazines, 1,4 substituted piperidines, and 1-substituted, 4-alkylidenyl piperidines.

Summary of the Related Art

Leukotrienes are potent local mediators, playing a major role in inflammatory and allergic responses including arthritis, asthma, psoriasis, and thrombotic disease. Leukotrienes are straight chain eicosanoids produced by the oxidation of arachidonic acid by lipoxygenases. Arachidonic acid is oxidized by 5-lipoxygenase and ultimately converted to leukotrienes A4, B4, C4 or D4. A mixture of one or more of such leukotrienes are known to be potent bronchoconstrictors. Thus, leukotrienes have been shown to play an important role in the pathology of asthma. Rigorous proof for the role of leukotrienes in asthma has been provided by several pivotal clinical trials in which orally administered single-acting 5-lipoxygenase (5-LO) inhibitors (or LTD4 receptor antagonists) produce clear therapeutic benefit in asthma patients. These benefits include reduction in the use of classic asthma therapies such as beta agonists and corticosteroids.

It is well known in the art that certain hydroxyurea- and hydroxyamide- substituted aromatic compounds can function as 5-LO inhibitors. For example, WO 92/09567 and WO 92/09566 disclose a wide variety of N-hydroxyurea and hydroxamic acid compounds as inhibitors of the lipoxygenase enzyme.

Histamine has been established to play a role in inflammation in general. Antihistamines are well established most notably for allergy control. Furthermore, histamine is believed to play a role in asthma. For example, histamine and cysteinyl leukotrienes (cLT's) are both known to be key mediators in airway tone. Clinical studies have shown that a combination therapy of a cLT

receptor antagonist and an antihistamine administered to twelve asthma patients, reduced early asthmatic responses (EAR) and late asthmatic responses (LAR) to a greater extent than either single-acting agent alone (A. Roquet, et al., *Am. J. Respir Crit. Care Med*, **155**, 1856 (1997)). This indicates that histamine plays a role in asthma.

It is well known that certain [bis(substituted and/or unsubstituted aryl) methyl- and methylene]-1-piperidyl compounds possess antihistaminergic activity, and numerous publications disclose such. For example, Yanni *et al.* (US 4,810,713 and 4,950,674) disclose [[bis(aryl)methyl- or methylene-]-1-piperidinyl]alkoxy -aryl and -heteroaryl compounds for the treatment of allergic phenomena, including asthma and rhinitis. Teng *et al.* (US 5,070,087) disclose [bis(aryl)methyl- and methylene]-N-[(phenoxy and phenylthio)alkyl]piperidines for countering effects of histamine in allergies.

Others have shown [bis(aryl)methyl]piperazin-1-yl compounds for use as antiasthmatics and antiallergics that inhibit leukotriene release (*e.g.*, JP 97077754). U.S. 4,525,358 teaches 2-[4-(diphenylmethyl)-1-piperazinyl]-acetic acid and their amides as antiallergic, spasmolytic, and antihistamine agents. JP 7138230 discloses 4-aralkyl-1-piperazinyl-unsaturated carboxylic acid derivatives useful an antiallergic agents for the treatment of, for example, asthma and rhinitis. WO 97/23466 describes the preparation of N-diarylmethylpiperazines as analgesics.

None of the art, however, teaches, suggests, or contemplates combining the 5-LO inhibiting functionality of hydroxyurea moieties with the antihistaminergic properties of [bis(substituted and/or unsubstituted aryl) methyl- and methylene]-1-piperidyl or –1-piperazinyl moieties in a single entity to yield a compound possessing the dual functions as an antihistaminergic and a 5-LO inhibitor.

SUMMARY OF THE INVENTION

The present invention provides novel compounds having dual properties, each compound possessing both 5-LO inhibition properties as well as antihistaminergic properties. In a preferred

embodiment, each of the novel compounds of the invention functions as both a 5-LO inhibitor as well as a histamine H1 receptor antagonist.

The compounds of the invention are useful for treating asthma and rhinitis. Accordingly, the invention also provides pharmaceutical compositions comprising the compounds of the invention and methods of treating asthma and rhinitis with the pharmaceutical compositions.

The compounds disclosed herein can also be used as research tools to study biological pathways involving both leukotrienes and histamine and, in particular, further elucidate the role histamine plays in bronchoconstriction.

All patent applications, patents, and other publications recited herein are hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 displays the synthesis of compound **1**.

Figure 2 displays the synthesis of compound **2**.

Figure 3 displays the synthesis of compound **3**.

Figure 4 displays the synthesis of compound **4**, **5**, and **6**.

Figure 5 displays the synthesis of compound **7**.

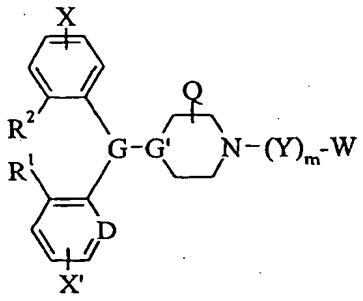
Figure 6 displays an alternative synthesis of compound **8**.

Figure 7 displays the synthesis of compound **50**.

DETAILED DESCRIPTION OF THE INVENTION

The Compounds

In one aspect, the present invention comprises compounds of formula I, including geometrical isomers, enantiomers, diastereomers, racemates, and pharmaceutically acceptable salts thereof:



I

wherein:

X and X′ independently are hydrogen, halo, alkyl, alkenyl, alkynyl, alkoxy, trifluoromethyl, or $-(Y')_{m'}-W'$;

G and G′ together form $\begin{matrix} \diagdown & \diagup \\ HC-N & \end{matrix}$, $\begin{matrix} \diagdown & \diagup \\ HC-CH & \end{matrix}$, or $\begin{matrix} \diagdown & \diagup \\ C=C & \end{matrix}$;

D is –CH= or =N-;

R^1 and R^2 independently are hydrogen or together are $-(CH_2)_n-$ in which n is equal to 0, 1, 2, or 3;

m and m′ independently are 0 or 1;

Y and Y′ are $-L^1-$ or $-L^2-V(Z)_t-L^3-$ in which t is 0 or 1;

L^1 is alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q)-, or $-N(R^3)-$;

L^2 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′)-, or $-N(R^4)-$, or (b) $-L^4-C(O)-N(Q')-$ or $-L^4(Q')-$, or (c) a direct bond;

L^3 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′)-, or $-N(R^5)-$, or (b) a direct bond;

L^4 is alkylene;

V is (a) a divalent arene, a divalent heteroarene, or a divalent saturated heterocycle when t is 0, or (b) a trivalent arene or trivalent heteroarene when t is 1;

Q, Q′, and Q′′ independently are hydrogen, -AC(O)OR^6, or -AC(O)NR^{6}R^7;

W and W′ independently are -N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, -N(OM)C(O)R^8, -C(O)N(OM)R^8, -C(O)NR^{8}R^9, or –C(O)OR^8, provided that at least one of W and W′ is –N(OM)C(O)N(R^8)R^9, -N(R^8)C(O)N(OM)R^9, -N(OM)C(O)R^8, or -C(O)N(OM)R^8;

Z is -N(OM′)C(O)N(R^{10})R^{11}, -N(R^{10})C(O)N(OM′)R^{11}, -N(OM′)C(O)R^{11}, -A′C(O)N(OM′)R^{11}, -A′C(O)NR^{10}R^{11}, or -A′C(O)OR^{10};

A and A′ independently are a direct bond, alkylene, alkenylene, alkynylene, yloalkylaryl, yloarylalkyl, or diyloalkylarene or one of the foregoing in which one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and/or one or more methylidenes are replaced by =N-;

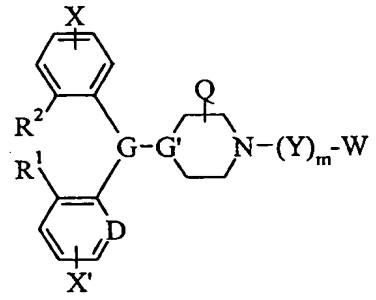
M and M′ independently are hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkylarylalkyl, or one of the foregoing in which one or more methylenes are replaced by -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and/or one or more methylidenes are replaced by =N-;

provided that, other than the oxygens bound to the sulfurs in -S(O)- and -S(O)$_2$-, when one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -S(O)$_2$- and when one or more methylidenes are placed with =N-, such replacement does not result in two heteroatoms being covalently bound to each other;

and further provided that when m is 0, W is -C(O)N(OM)R^8, -C(O)NR^{8}R^9, or –C(O)OR^8.

Preferably, compounds of the present invention are those having formula II′:



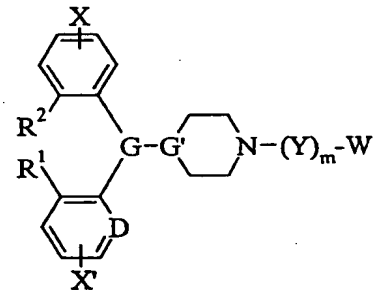
I′

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above, except that:

X and X′ independently are -H, halo, alkyl, alkenyl, alkynyl, alkoxy, or trifluoromethyl; and

W is $-N(OM)C(O)N(R^8)R^9$, $-N(R^8)C(O)N(OM)R^9$, $-N(OM)C(O)R^8$, or $-C(O)N(OM)R^8$.

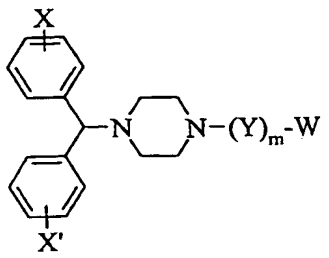
In another preferred embodiment, the compounds of the present invention are given by formula I′′:



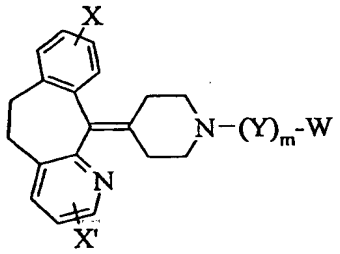
I′′

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above.

In other preferred embodiments, compounds of formula I are represented by the following formulas, II and III:



II



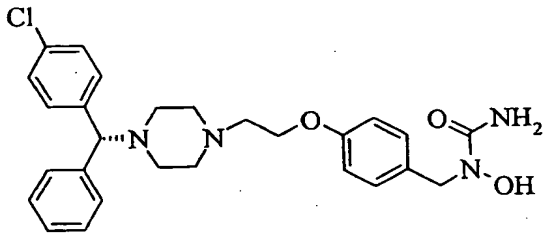
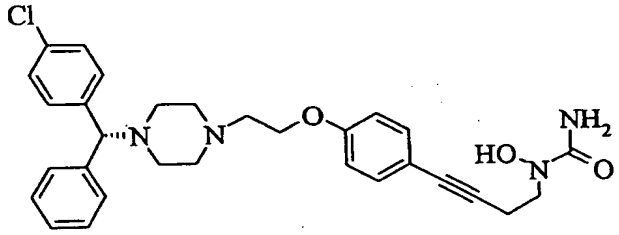
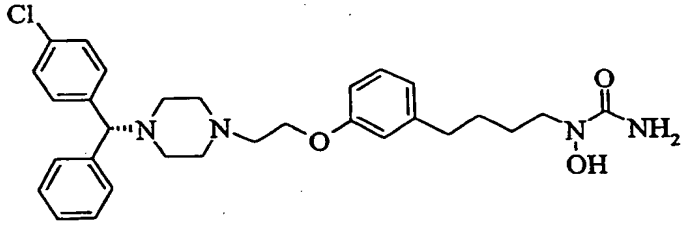
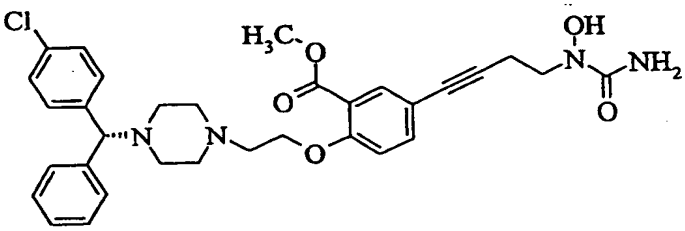
III

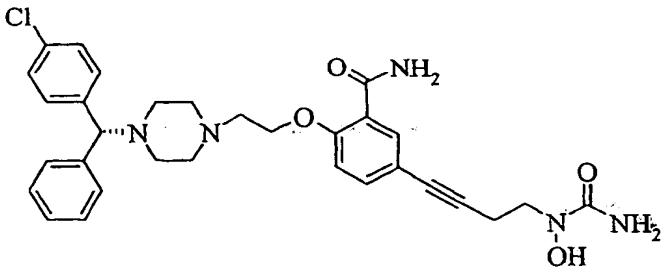
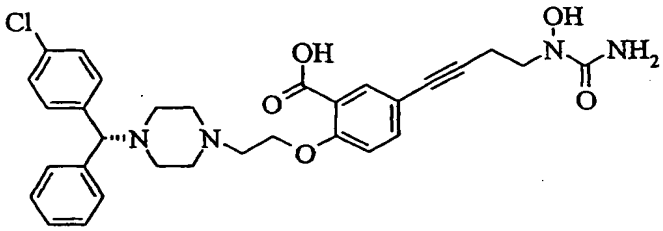
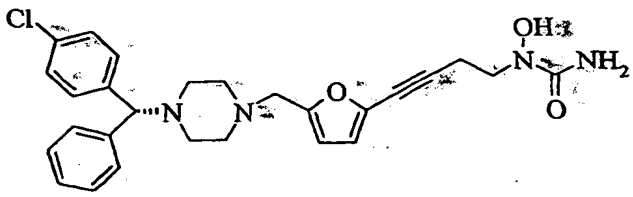
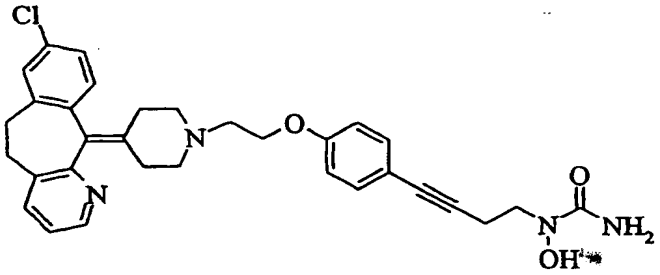
and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above.

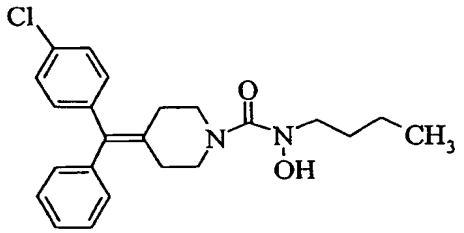
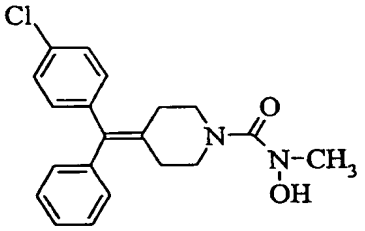
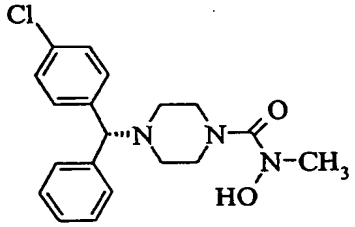
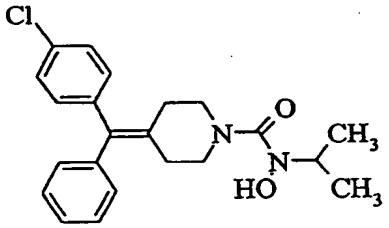
More preferred embodiments of the compounds of formula II and III and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein each of the variables is as defined above except that:

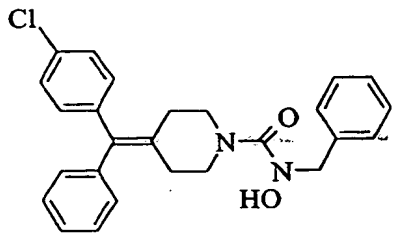
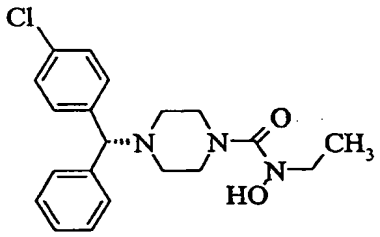
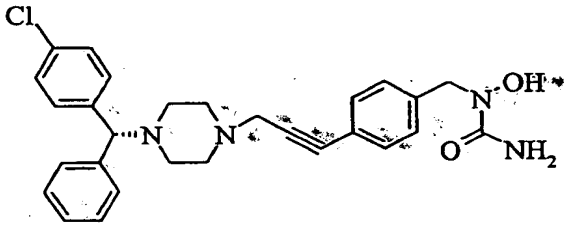
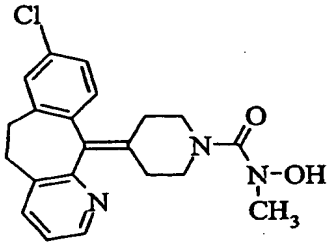
1. X is -Cl, X′ is hydrogen, m is 0 and W is $-C(O)N(OH)-R^3$;
2. X is -Cl, X′ is hydrogen, m is 1 and W is $-N(OH)C(O)NH_2$;
3. X is -Cl, X′ is hydrogen, m is 1, Y is $-L^1-$, wherein L^1 is alkynylene, yloalkoxy, or yloalkoxyalkyl;
4. X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V-L^3-$, t is 0, V is 1,4-phenylene or 1,3-phenylene, L^2 is yloalkoxy, and L^3 is alkylene, alkenylene, or alkynylene;
5. X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V-L^3-$, t is 0, V is 2,5-furylene, L^2 is alkylene, and L^3 is alkylene, alkenylene, or alkynylene; or
6. X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 1, L^2 is yloalkoxy, V is trivalent heteroarene, Z is $-AC(O)NR^3R^4$ or $-AC(O)OR^3$, and W is $-N(OH)C(O)NH_2$.

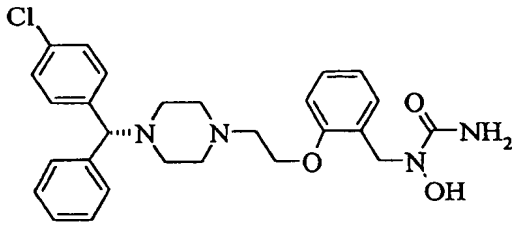
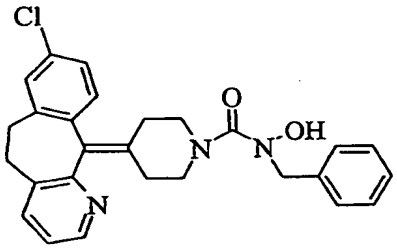
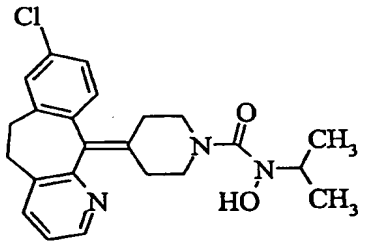
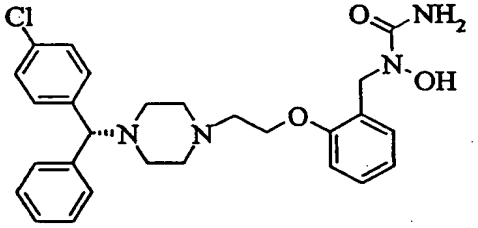
Compounds of the invention include:

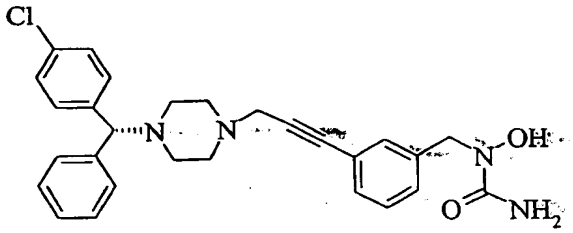
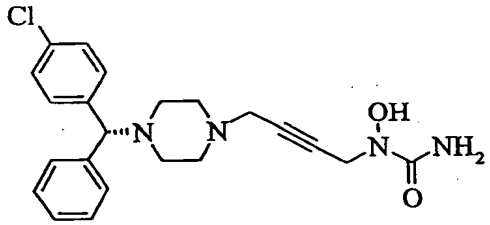
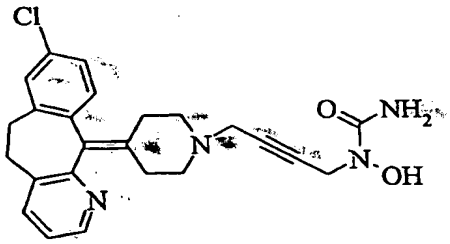
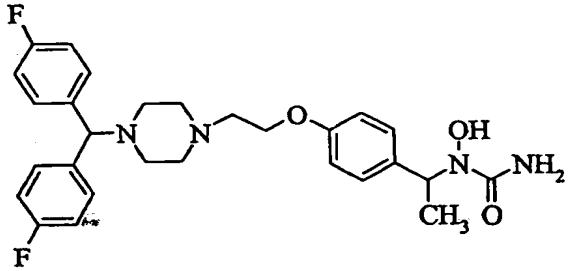
Cpd #	Structure and Name
1	 N-{[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] Piperazinyl}ethoxy)phenyl]methyl}amino-N-hydroxyamide
2	 N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide
3	 N-{4-[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]butyl}amino-N-hydroxyamide
4	 methyl 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl amino)but-1-ynyl]benzoate

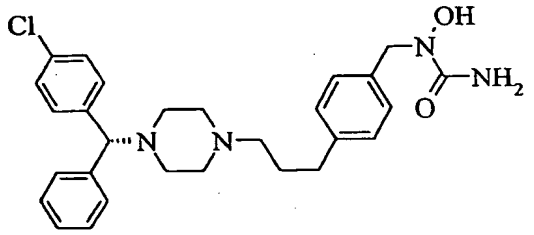
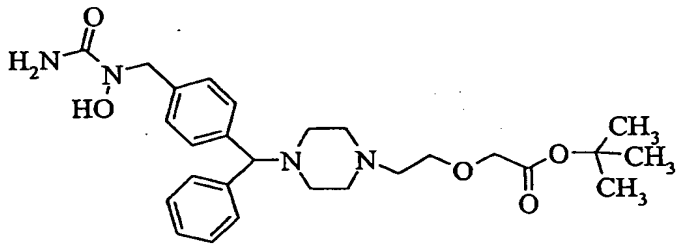
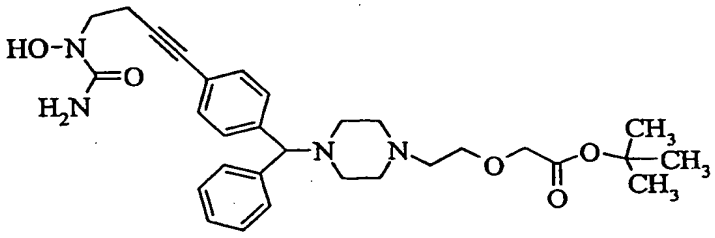
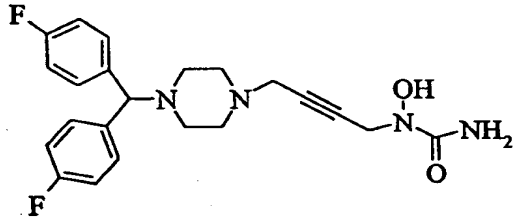
Cpd #	Structure and Name
5	 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl amino)but-1-ynyl]benzamide
6	 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoic acid
7	 N-{4-[5-({4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}methyl)(2-furyl)]but-3-ynyl}amino-N- hydroxyamide
8	 N-[4-(4-{2-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7] annulen-11-ylidene))piperidyl]ethoxy}phenyl)but-3-ynyl]-amino-N-hydroxyamide

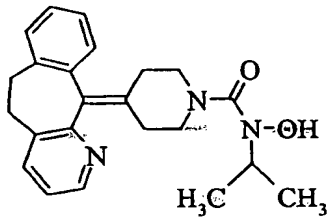
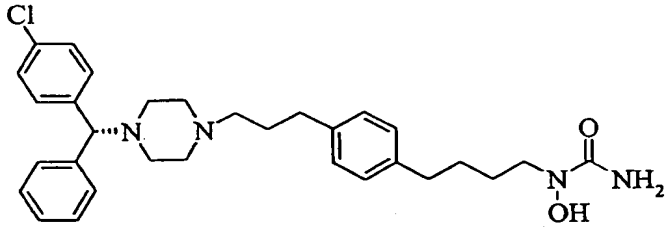
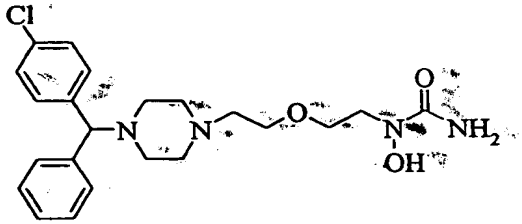
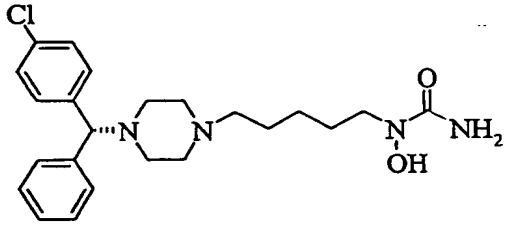
Cpd #	Structure and Name
9	 N-butyl{4-[(4-chlorophenyl)phenylmethylene]piperidyl}-N-hydroxycarboxamide
10	 {4-[(4-chlorophenyl)phenylmethylene]piperidyl}-N-hydroxy-N-methylcarboxamide
11	 {4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}-N-hydroxy-N-methylcarboxamide
12	 {4-[(4-chlorophenyl)phenylmethylene] piperidyl}-N-hydroxy-N-(methylethyl)carboxamide

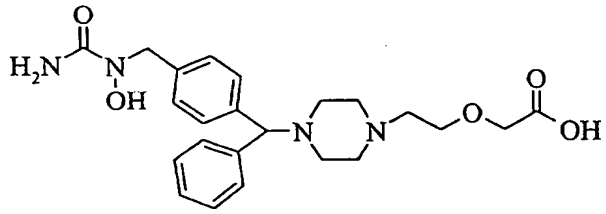
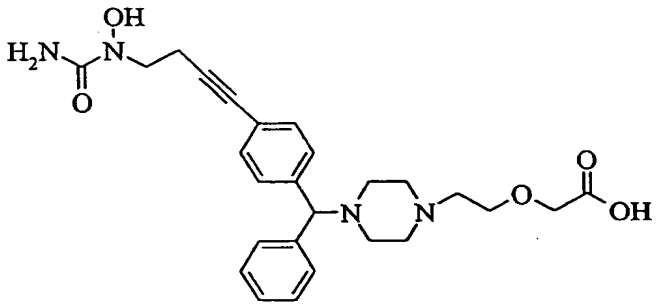
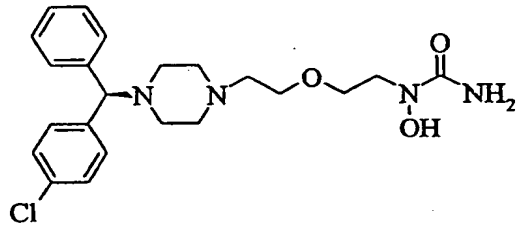
Cpd #	Structure and Name
13	 {4-[(4-chlorophenyl)phenylmethylene]piperidyl}-N-hydroxy-N-benzylcarboxamide
14	 {4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}-N-ethyl-N-hydroxycarboxamide
15	 N-{[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl] Piperazinyl}prop-1-ynyl)phenyl]methyl}amino-N-hydroxyamide
16	 [4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7] annulen-11-ylidene))piperidyl]-N-hydroxy-N-methylcarboxamide

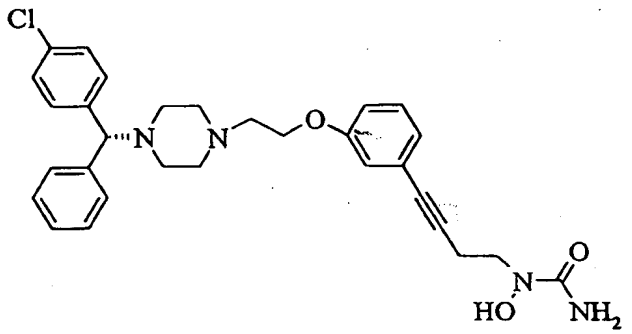
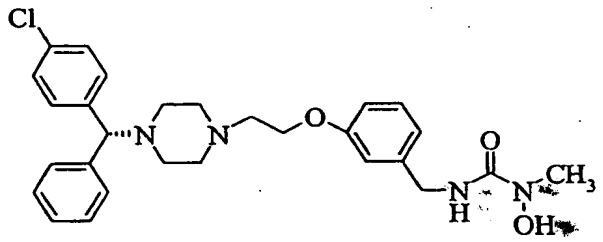
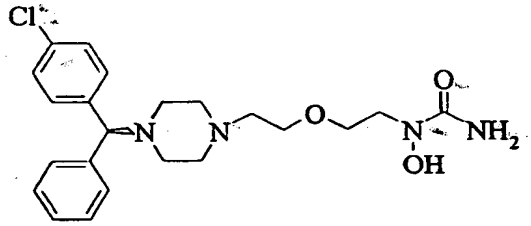
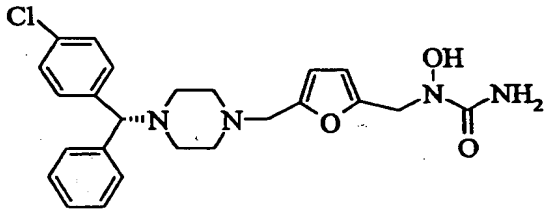
Cpd #	Structure and Name
17	 N-{[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]methyl}amino-N-hydroxyamide
18	 [4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7] annulen-11-ylidene))piperidyl]-N-hydroxy-N-benzylcarboxamide
19	 [4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b][7] annulen-11-ylidene))piperidyl]-N-hydroxy-N-(methylethyl)carboxamide
20	 N-{[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]methyl}amino-N-hydroxyamide

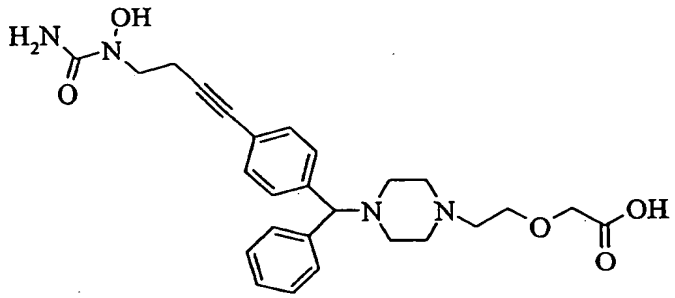
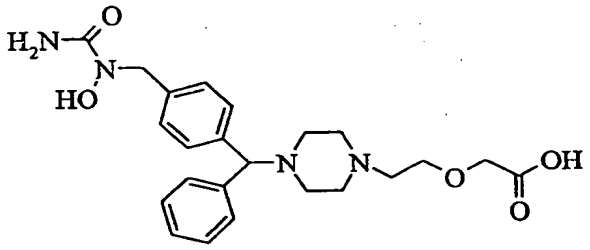
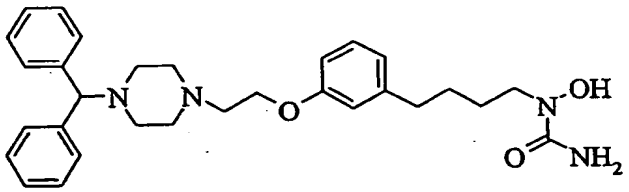
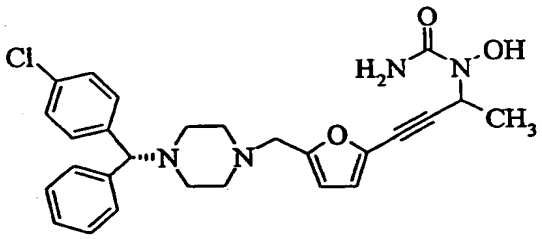
Cpd #	Structure and Name
21	 N-{[3-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl] Piperazinyl}prop-1-ynyl)phenyl]methyl}amino-N-hydroxyamide
22	 N-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}but-2-ynyl)amino-N-hydroxyamide
23	 N-{4-[4-(8-chloro(5,6-dihydrobenzo[f]pyridino[2,3-b] [7]annulen-11-ylidene))piperidyl]but-2-ynyl}-amino-N-hydroxyamide
24	 N-{[4-(2-{4-[bis(4-fluorophenyl)methyl] piperazinyl}ethoxy)phenyl]ethyl}-amino-N-hydroxyamide

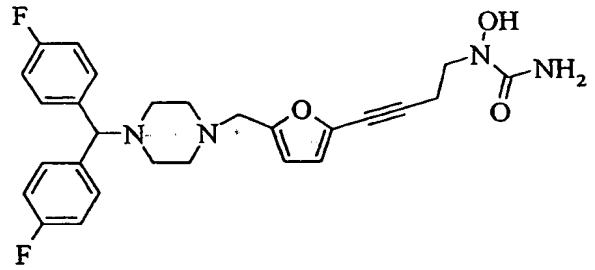
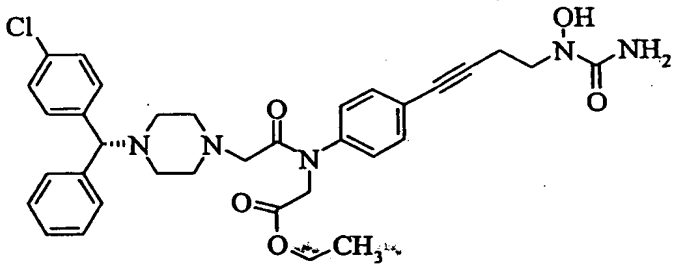
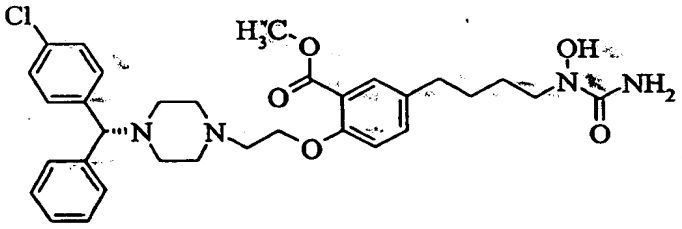
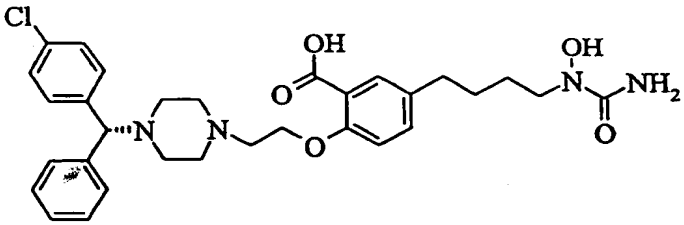
Cpd #	Structure and Name
25	 N-{[4-(3-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}propyl)phenyl]methyl}amino-N-hydroxyamide
26	 tert-butyl 2-{2-[4-({4-[(aminohydroxycarbonylamino) methyl]phenyl}phenylmethyl)piperazinyl]ethoxy}acetate
27	 tert-butyl 2-{2-[4-({4-[4-(aminohydroxycarbonylamino) but-1-ynyl]phenyl}phenylmethyl)piperazinyl]ethoxy}acetate
28	 N-(4-{4-[bis(4-fluorophenyl)methyl]piperazinyl}but-2-ynyl)-amino-N-hydroxyamide

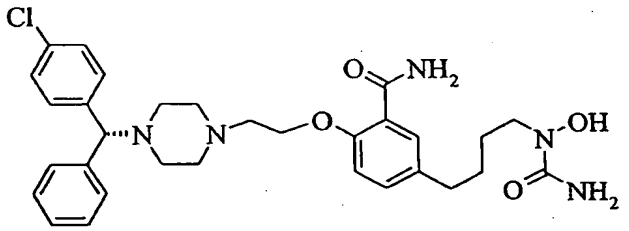
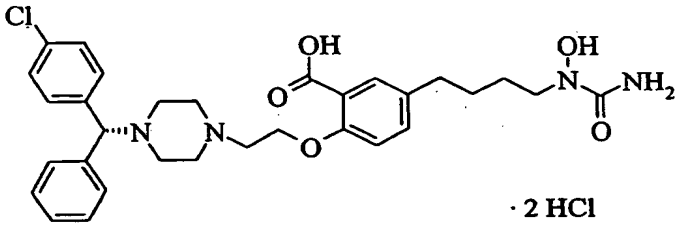
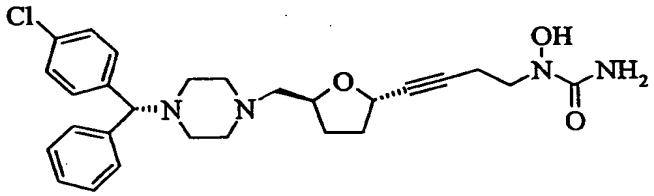
Cpd #	Structure and Name
29	 (4-(5,6-dihydrobenzo[f]pyridino[2,3-b][7]annulen-11-ylidene)piperidyl)-N-hydroxy-N-(methylethyl)carboxamide
30	 N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]butyl}amino-N-hydroxyamide
31	 amino-N-[2-(2-{4-[(4-chlorophenyl)phenyl-methyl]piperazinyl}ethoxy)ethyl]-N-hydroxyamide
32	 N-(4-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}butyl)amino-N-hydroxyamide

Cpd #	Structure and Name
33	 2-{2-[4-({4-[(aminohydroxycarbonylamino)methyl] phenyl}phenylmethyl)piperazinyl]ethoxy}acetic acid
34	 2-{2-[4-({4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}phenylmethyl)piperazinyl]ethoxy}acetic acid
35	 N-[2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)ethyl]-amino-N-hydroxyamide

Cpd #	Structure and Name
36	 N-{4-[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]but-3-ynyl}amino-N-hydroxyamide
37	 N-{[3-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]methyl}(methyl(hydroxyamino))carboxamide
38	 N-[2-(2-{4-[(1S)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)ethyl]-amino-N-hydroxyamide
39	 N-{[5-({4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}methyl)(2-furyl)]methyl}amino-N-hydroxyamide

Cpd #	Structure and Name
40	 2-{2-[4-({4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}phenylmethyl)piperazinyl]ethoxy}acetic acid
41	 2-{2-[4-({4-[(aminohydroxycarbonylamino)methyl]phenyl}phenylmethyl)piperazinyl]ethoxy}acetic acid
42	 N-[4-(3-{2-[4-(diphenylmethyl)piperazinyl]ethoxy}phenyl)butyl]-amino-N-hydroxyamide
43	 N-{3-[5-({4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}methyl)(2-furyl)]-1-methylprop-2-ynyl}amino-N-hydroxyamide

Cpd #	Structure and Name
44	 N-{4-[5-({4-[bis(4-fluorophenyl)methyl]piperazinyl}methyl)(2-furyl)]but-3-ynyl}-amino-N-hydroxyamide
45	 ethyl 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}-N-{4-[4-(aminohydroxycarbonylamino)but-1-ynyl]phenyl}acetylamino)acetate
46	 methyl 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzoate
47	 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzoic acid

Cpd #	Structure and Name
48	 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzamide
49	 · 2 HCl 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl} ethoxy)-5-[4-(aminohydroxycarbonylamino)butyl]benzoic acid • 2 HCl
50	 N-{4-[5-({4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}methyl)(2S,5S)oxolan-2-yl]but-3-ynyl}amino-N-hydroxyamide

Particularly preferred compounds are those listed in Table 1, *infra*.

More preferred are compounds **2, 4, 5, 6,** and **30** and compounds **1, 7, 8, 36,** and **44.**

Definitions

The following paragraphs provide definitions of the various chemical moieties that make up the compounds of the invention and are intended to apply uniformly throughout the specification and claims unless expressly stated otherwise.

The term alkyl refers to a univalent C_1 to C_6 saturated straight, branched, or cyclic alkane moiety and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The alkyl group can be optionally substituted with any appropriate group, including but not limited to R^3 or one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art or as taught, for example, in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991.

The term alkoxy refers to an alkyl moiety having a terminal –O- with free a valence, *e.g.*, CH_3CH_2-O-;

The term yloalkoxy is an alkoxy (as defined above) in which a hydrogen atom has been removed from the alkyl moiety to yield a divalent radical, *.e.g.*, -CH_2CH_2O- or –$CH(CH_3)O$-.

The term yloalkoxyalkyl refers to a divalent, dialkyl ether moiety having one free valence on each of the alkyl moieties, which alkyl moieties are the same or different, *e.g.*, -$CH_2CH_2CH_2$-O-CH_2-.

The term alkylene refers to an alkyl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -$CH_2CH(CH_3)CH_2CH_2$-.

The term alkenyl refers to a univalent C_2-C_6 straight, branched, or in the case of C_{5-6}, cyclic hydrocarbon with at least one double bond, optionally substituted as described above.

The term alkenylene refers to an alkenyl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -CH_2CH=$CHCH_2$-.

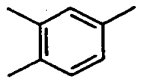
The term alkynyl refers to a univalent C_2 to C_6 straight or branched hydrocarbon with at least one triple bond (optionally substituted as described above) and specifically includes acetylenyl, propynyl, and -C≡C-CH_2(alkyl), including -C≡C-$CH_2(CH_3)$.

The term alkynylene refers to an alkynyl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -C≡C-CH(CH_3)-.

The term aryl refers to a univalent phenyl (preferably), biphenyl, or napthyl. The aryl group can be optionally substituted with any suitable group, including but not limited to one or more moieties selected from the group consisting of halo, hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, et al., "Protective Groups in Organic Synthesis," John Wiley and Sons, Second Edition, 1991, and preferably with halo (including but not limited to fluoro), alkoxy (including methoxy), aryloxy (including phenoxy), W, cyano, or R^3.

The terms arylene and divalent arene refer to an aryl moiety (as defined above) in which a hydrogen atom has been removed to yield a divalent radical, *e.g.*, -C_6H_4-.

The term trivalent arene refers to an arylene moiety (as defined above) in which a hydrogen atom has been removed to yield a trivalent radical, *e.g.*,



The term yloalkylaryl refers to a divalent alkyl-substituted aryl moiety in which one open valence is on the alkyl moiety and one is on the aryl moiety, *e.g.*, -CH_2-CH_2-C_6H_4-.

The term yloarylalkyl refers to a divalent aryl-substituted alkyl moiety in which one open valence is on the alkyl moiety and one is on the aryl moiety, *e.g.*, -C_6H_4-CH_2-CH_2-.

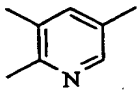
The term diylodialkylarene refers to a divalent, dialkyl-substituted arene in which there is one open valence on each of the alkyl moieties (which may be the same or different), *e.g.*, -CH_2-C_6H_4-CH_2CH_2-.

The term heteroatom means O, S, or N.

The term heterocycle refers to a cyclic alkyl, alkenyl, or alkynyl moiety as defined above wherein one or more ring carbon atoms is replaced with a heteroatom.

The terms heteroarylene and divalent heteroarene refer to an arylene (or divalent heteroarene) that includes at least one sulfur, oxygen, or nitrogen in the aromatic ring, which can optionally be substituted as described above for the aryl groups. Non-limiting examples are pyrrylene, furylene, pyridylene, 1,2,4-thiadiazolylene, pyrimidylene, thienylene, isothiazolylene, imidazolylene, tetrazolylene, pyrazinylene, pyrimidylene, quinolylene, isoquinolylene, benzothienylene, isobenzofurylene, pyrazolylene, indolylene, purinylene, carbazolylene, benzimidazolylene, and isoxazolylene.

The term trivalent heteroarene refers to a heteroarylene moiety (as defined above) in which a hydrogen atom has been removed to yield a trivalent radical, *e.g.*,



The term halo refers to chloro, fluoro, iodo, or bromo.

When a methylene of an alkyl, alkenyl, or alkynyl (or their divalent radical counterparts) is replaced by O, -NH-, -S-, -S(O)-, or -$S(O)_2$-, it may be at any suitable position in the moiety, either at the terminal or internal positions, *e.g.*, CH_3CH_2-O-, CH_3-O-CH_2-, CH_3CH_2NH-, and CH_3NHCH_2-.

Open valences on the radical moieties described herein can occur on any one (or more for divalent radicals) of the atoms within the moiety. For example, the monovalent C_3 alkyl moiety includes both propyl and isopropyl. As another example, the divalent C_4 alkylene moiety includes both tetramethylene (-$CH_2(CH_2)_2CH_2$-) and ethylethylene (-$CH(CH_2CH_3)CH_2$-).

The term organic or inorganic anion refers to an organic or inorganic moiety that carries a negative charge and can be used as the negative portion of a salt.

The term "pharmaceutically acceptable cation" refers to an organic or inorganic moiety that carries a positive charge and that can be administered in association with a pharmaceutical agent, for example, as a countercation in a salt. Pharmaceutically acceptable cations are known to those of skill in the art, and include but are not limited to sodium, potassium, and quaternary ammonium.

The term "metabolically cleavable group" refers to a moiety that can be cleaved *in vivo* from the molecule to which it is attached, and includes but is not limited to an organic or inorganic anion, a pharmaceutically acceptable cation, acyl (for example (alkyl)C(O), including acetyl, propionyl, and butyryl), alkyl, phosphate, sulfate and sulfonate.

The term 5-lipoxygenase inhibitor refers to a compound that inhibits the enzyme at 30 μM or lower.

As used herein, the term pharmaceutically acceptable salts or complexes refers to salts or complexes that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula -NR + Z-, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamoate, mandeloate, benzyloate, and diphenylacetate).

The term pharmaceutically active derivative refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein.

Synthetic Schemes

The synthetic schemes displayed in Figs. 1-6 illustrate how compounds according to the invention can be made. Those skilled in the art will be able to routinely modify and/or adapt the following schemes to synthesize any compound of the invention.

Pharmaceutical Compositions, Methods of Treatment and Administration

The compounds of the invention are useful as anti-inflammatory, antirhinitis, antiallergic, antihistaminic, bronchodilatory and antispasmodic agents and are particularly useful in the treatment of asthma and rhinitis. The compounds exhibit this biological activity by acting as histamine H1 receptor antagonists, by inhibiting the enzyme 5-lipoxygenase, or by exhibiting dual activity, *i.e.*, by acting as both a histamine H1 receptor antagonist and inhibitor of 5-lipoxygenase.

Subjects in need of treatment for a leukotriene-mediated and/or histamine-mediated condition (preferably, asthma) can be treated by administering to the patient an effective amount of one or more of the above-identified compounds or a pharmaceutically acceptable derivative or salt thereof in a pharmaceutically acceptable carrier or diluent to reduce formation of oxygen radicals. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid, cream, gel or solid form, via a buccal or nasal spray, or aerosol.

The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective

dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

The methods of the invention comprise administration to a mammal (preferably human) suffering from a leukotriene-mediated and/or histamine-mediated condition (preferably, asthma and rhinitis) a pharmaceutical composition according to the invention in an amount sufficient to alleviate the condition. The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 1 to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. A oral dosage of 1–500, preferably 10-250, more preferably 25-250 mg is usually convenient.

The active ingredient should be administered to achieve peak plasma concentrations of the active compound of about 0.001–30 μM, preferably about 0.01–10 μM. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic

administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterores; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents.

The active compound or pharmaceutically acceptable salt or derivative thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active compound or pharmaceutically acceptable derivatives or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, other anti-inflammatories, or antiviral compounds.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as

sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation (CA) and Gilford Pharmaceuticals (Baltimore, Md.). Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidylcholine, arachadoyl phosphatidylcholine, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

The following Examples are provided for illustrative purposes only and are not intended, nor should they be construed, as limiting the invention in any manner. Those skilled in the art will appreciate that routine variations and modifications of the following Examples can be made without exceeding the spirit or scope of the invention.

EXAMPLES

Example 1

Preparation of N-{[4-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl] methyl}-amino-N-hydroxyamide (compound 1, Figure 1)

4-(2-Bromoethoxy)benzylalcohol (compound 101)

To a solution of 4-hydroxybenzylalcohol (2.0 g, 16.11 mmol) in DMF (10 mL) was added potassium carbonate (2.67 g, 19.32 mmol). The reaction was stirred at room temperature for 30 minutes and then 1,2-dibromoethane (3.03 g, 16.13 mmol) was added. The reaction was stirred at room temperature for additional 20 hours and then quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, evaporated to yield an oil which was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield 101 (1.7 g, 45.7%): ^{1}H NMR ($CDCl_3$) δ 3.64 (t, 2H), 4.29 (t, 2H), 4.62 (s, 2H), 6.91 (d, 2H), 7.30 (d, 2H).

4-{2-[4-((1R)(4-Chlorophenyl)phenylmethyl)piperazinyl]ethoxy}benzylalcohol (compound 103)

To a solution of 101 (205 mg, 0.89 mmol), [(1R)(4-chlorophenyl) phenylmethyl]-piperazine (102) (230 mg, 0.80 mmol) in dichloromethane (2.5 mL) was added triethylamine (122.0 mg, 1.21 mmol). The reaction was stirred at 50° C for 20 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield 103 (330 mg, 94.1%): ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 4H), 2.62 (m, 4H), 2.81 (t, 2H), 4.08 (t, 2H), 4.22 (s, 1H), 4.51 (s, 2H), 6.87 (d, 2H), 7.28 (m, 6H), 7.39 (m, 5H).

N-{[4-(2-{4-[(1R)(4-Chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}phenoxy-carbonylaminophenoxyformate (compound 104)

To a stirred solution of 103 (330 mg, 0.76 mmol), phenoxycarbonylamino-phenoxyformate (251.6 mg, 0.92 mmol) and triphenylphosphine (225.2 mg, 0.86 mmol) in THF (8 mL) at 0° C was added diisopropylazodicarboxylate (174.1 mg, 0.86 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel,

2:1 hexane/ethyl acetate) to give **104** (410 mg, 78.4%): ^{1}H NMR ($CDCl_3$) δ 2.47 (m, 4H), 2.65 (m, 4H), 2.84 (t, 2H), 4.12 (t, 2H), 4.23 (s, 1H), 4.95 (s, 2H), 6.92 (d, 2H), 7.20 (m, 5H), 7.26 (m, 6H), 7.40 (m, 10H).

N-{[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)phenyl]methyl}-amino-N-hydroxyamide (compound **1**)

In a screw top vessel was placed a solution of **104** (410 mg, 0.59 mmol) in methanol (15 mL) and cooled to -78° C with dry ice-acetone bath. To this vessel was added liquid NH_3 (2-3 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure released. The vessel was opened and the solvent was evaporated. Compound **1** was separated by flash column chromatography (silica gel, 19:1 CH_2Cl_2/CH_3OH) (215 mg, 73.2%): ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 4H), 2.59 (m, 4H), 2.74 (t, 2H), 3.98 (t, 2H), 4.20 (s, 1H), 4.57 (s, 2H), 5.22 (bs, 2H), 6.77 (d, 2H), 7.25 (m, 6H), 7.36 (m, 5H).

Example 2

Preparation of N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl}ethoxy)phenyl]but-3-ynyl}-amino-*N-hydroxyamide (compound 2, Figure 2)*

4-(2-Bromoethoxy)-1-iodobenzene (compound **105**)

To a solution of 4-iodophenol (10.0g, 45.45 mmol) in DMF (50 mL) was added potassium carbonate (12.6 g, 91.17 mmol). The reaction was stirred at room temperature for 30 minutes and then 1,2-dibromoethane (17.07 g, 90.91 mmol) was added. The reaction was stirred at room temperature for additional 16 hours and then quenched with water and extracted with dichloromethane. The organic layer was washed with water and brine, evaporated to yield an oil which was purified by flash column chromatography (silica gel, hexane) to yield **105** (2.7 g, 18.2%): ^{1}H NMR ($CDCl_3$) δ 3.63 (t, 2H), 4.26 (t, 2H), 6.70 (d, 2H), 7.58 (d, 2H).

4-[4-(2-Bromoethoxy)phenyl]but-3-yn-1-ol (compound 106)

To a mixture of **105** (2.7 g, 8.26 mmol), 3-butyn-1-ol (696.3 mg, 9.94 mmol), dichlorobis(triphenylphosphine)palladium(II) (1.15 g, 1.64 mmol) and cuprous iodide (317.1 mg, 1.67 mmol) was added triethylamine (45 mL). The reaction was stirred at room temperature for 16 hours. The solvent was evaporated and the residue purified by flash column chromatography (silica gel, 3:1 hexane/ethyl acetate) to yield **106** (1.3 g, 58.6%): ^{1}H NMR ($CDCl_3$) δ 2.70 (m, 4H), 3.65 (t, 2H), 3.82 (m, 2H), 4.30 (t, 2H), 6.83 (d, 2H), 7.37 (d, 2H).

4-{4-[2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy] phenyl} but-3-yn-1-ol (compound 107)

To a solution of **106** (1.5 g, 5.58 mmol), [(1R)(4-chlorophenyl)phenylmethyl]piperazine (102) (1.6 g, 5.59 mmol) in DMF (15 mL) was added triethylamine (871.2 mg, 8.63 mmol). The reaction was stirred at 50° C for 20 hours, water was added, and the reaction was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to an oil which was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield **107** (2.6 g, 98.1%): ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 4H), 2.61 (m, 4H), 2.68 (t, 2H), 2.82 (t, 2H), 3.80 (t, 2H), 4.10 (t, 2H), 4.21 (s, 1H), 6.80 (d, 2H), 7.26 (m, 5H), 7.35 (m, 6H).

N-{4-[4-(2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy) phenyl] but-3-ynyl} phenoxycarbonylaminophenoxyformate (compound 108)

To a stirred solution of **107** (1.5 g, 3.16 mmol), phenoxycarbonylaminophenoxyformate (1.05 g, 3.85 mmol) and triphenylphosphine (937.1 mg, 3.57 mmol) in THF (35 mL) at 0° C was added diisopropylazodicarboxylate (721.4 mg, 3.57 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give **108** (1.4 g, 60.6%): ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 4H), 2.62 (m,

4H), 2.82 (m, 2H), 2.91 (t, 2H), 4.10 (m, 4H), 4.21 (s, 1H), 6.80 (d, 2H), 7.18 (m, 5H), 7.30 (m, 8H), 7.37 (m, 8H).

N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl] but-3-ynyl}-Amino-N-hydroxyamide (compound 2)

In a screw top vessel was placed a solution of 108 (1.4 g, 1.92 mmol) in methanol (50 mL) and cooled to -78° C with dry ice-acetone bath. To this vessel was added liquid NH_3 (6 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure released. The vessel was opened and the solvent evaporated. Compound 2 was separated by flash column chromatography (silica gel, 19:1 CH_2Cl_2/CH_3OH) (580 mg, 56.9%): ^1H NMR ($CDCl_3$) δ 2.45 (m, 4H), 2.65 (m, 4H), 2.72 (t, 2H), 2.84 (t, 2H), 3.80 (t, 2H), 4.10 (t, 2H), 4.22 (s, 1H), 5.25 (bs, 2H), 6.80 (d, 2H), 7.25 (m, 5H), 7.36 (m, 6H).

Example 3

Preparation of N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl]butyl}-amino-N-hydroxyamide (compound 3, Figure 3)

4-[4-(2-Bromoethoxy)phenyl]butan-1-ol (compound **109**)

A solution of **106** (1.3 g, 4.83 mmol) in methanol (15 mL) was hydrogenated over 10% palladium on charcoal (130 mg) at balloon pressure for 7 hours. The catalyst was filtered off and the filtrate was evaporated to give **109** (1.31 g, 99.2%): ^1H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.60 (t, 2H), 3.66 (m, 4H), 4.28 (m, 2H), 6.83 (d, 2H), 7.10 (d, 2H).

4-{4-[2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy] phenyl} butan-1-ol (compound **110**)

To a solution of **109** (1.3 g, 4.76 mmol) and [(1R)(4-chlorophenyl)phenylmethyl]piperazine (**102**) (1.39 g, 4.86 mmol) in DMF (12 mL) was added triethylamine (762.3 mg, 7.55 mmol). The reaction was stirred at 50° C for 16 hours, water was added, and the reaction was extracted with dichloromethane. The organic layer was washed with

water and brine, dried over magnesium sulfate, filtered, and evaporated to an oil, which was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to yield 110 (2.42 g, 104%): ^{1}H NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.45 (m, 4H), 2.62 (m, 6H), 2.81 (t, 2H), 3.66 (t, 2H), 4.08 (t, 2H), 4.21 (s, 1H), 6.81 (d, 2H), 7.08 (d, 2H), 7.25 (m, 4H), 7.36 (m, 5H), 8.02 (bs, 1H).

N-{4-[4-(2-(4-((1R) (4-Chlorophenyl) phenylmethyl) piperazinyl) ethoxy) phenyl] butan-1-ol} phenoxycarbonylaminophenoxyformate (compound 111)

To a stirred solution of 110 (1.5 g, 3.14 mmol), phenoxycarbonylaminophenoxyformate (1.05 g, 3.85 mmol) and triphenylphosphine (938.0 mg, 3.58 mmol) in THF (35 mL) at 0° C was added diisopropylazodicarboxylate (724.0 mg, 3.58 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to give 111 (1.58 g, 68.7%).

N-{4-[4-(2-{4-[(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) phenyl] butyl}-amino-N-hydroxyamide (compound 3)

In a screw top vessel was placed a solution of 111 (1.58 g, 2.16 mmol) in methanol (50 mL) and cooled to -78° C in a dry ice-acetone bath. To this vessel was added liquid ammonia (6 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure was released. The vessel was opened and the solvent was evaporated. Compound 3 was separated by flash column chromatography (silica gel, 19:1 CH_2Cl_2/CH_3OH) and further purified by recrystallization using ethyl acetate-hexane as a solvent (550 mg, 47.4%): ^{1}H NMR ($CDCl_3$) δ 1.60 (m, 4H), 2.44 (m, 4H), 2.52 (t, 2H), 2.67 (m, 4H), 2.83 (t, 2H), 3.48 (t, 2H), 4.08 (t, 2H), 4.21 (s, 1H), 6.78 (d, 2H), 7.04 (d, 2H), 7.25 (m, 4H), 7.35 (m, 5H).

Example 4

Preparation of methyl-2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoate (compound 4, Figure 4), 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonylamino) but-1-ynyl] benzamide (compound 5, Figure 4), and 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl] piperazinyl} ethoxy)-5-[4-(aminohydroxycarbonylamino)but-1-ynyl]benzoic acid (compound 6, Figure 4)

4-iodophenol, methyl acetate (compound 112)

To a solution of 5-iodosalicylic acid (5.0 g, 18.94 mmol) in methanol (100 mL) was added a few drop of sulfuric acid. The reaction was stirred at reflux for 24 hours. The reaction solvent (methanol) was evaporated to small volume and water was added and extracted with dichloromethane. The organic layer was washed with 10% $NaHCO_3$ solution, water and brine, dried over magnesium sulfate, filtered and evaporated to give the title compound (3.5 g, 66.5%): ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H), 6.78 (d, 1H), 7.70 (dd, 1H), 8.12 (d, 1H).

Methyl 2-hydroxy-5-(4-hydroxybut-1-ynyl)benzoate (compound 113)

To a mixture of **112** (2.0 g, 7.19 mmol), 3-butyn-1-ol (655.2 mg, 9.35 mmol), dichlorobis(triphenylphosphine)palladium(II) (1.0 g, 1.42 mmol) and cuprous iodide (276.3 mg, 1.45 mmol) was added triethylamine (40 mL). The reaction was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to yield 113 (1.6 g, 101.3%): ^1H NMR ($CDCl_3$) δ 2.68 (t, 2H), 3.81 (m, 2H), 3.96 (s, 3H), 6.92 (d, 1H), 7.50 (dd, 1H), 7.93 (d, 1H).

Methyl 2-(2-bromoethoxy)-5-(4-hydroxybut-1-ynyl)benzoate (compound 114)

To a solution of **113** (1.6 g, 7.27 mmol) in DMF (8 mL) was added potassium carbonate (1.51 g, 10.91 mmol). The reaction was stirred at room temperature for 30 minutes and then 1,2-dibromoethane (5.47 g, 29.09 mmol) was added. The reaction was stirred at room temperature for additional 16 hours and then quenched with water and extracted with dichloromethane. The organic layer was washed with water and brine, evaporated to yield an oil which was purified by flash column chromatography (silica gel, 2:1 hexane/ethyl acetate) to yield **114** (710 mg, 29.8%):

^{1}H NMR ($CDCl_3$) δ 2.70 (t, 2H), 3.68 (t, 2H), 3.82 (t, 2H), 3.90 (s, 3H), 4.35 (t, 2H), 6.90 (d, 1H), 7.50 (dd, 1H), 7.88 (d, 1H).

Methyl 2-(2-{4-[(1R)(4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy)-5-(4-hydroxybut-1-ynyl)benzoate (compound 115)

To a solution of **114** (300.0 mg, 0.92 mmol), [(1R)(4-chlorophenyl) phenylmethyl] piperazine (**102**) (262.4 mg, 0.92 mmol) in DMF (2 mL) was added triethylamine (139.0 mg, 1.38 mmol). The reaction was stirred at 50° C for 20 hours, water was added, and the reaction was extracted with dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and evaporated to an oil which was purified by flash column chromatography (silica gel, ethyl acetate) to yield **115** (510 mg, 102.4%): ^{1}H NMR ($CDCl_3$) δ 2.44 (m, 4H), 2.68 (m, 6H), 2.90 (m, 2H), 3.81 (t, 2H), 3.84 (s, 3H), 4.08 (m, 2H), 4.21 (s, 1H), 6.90 (d, 1H), 7.25 (m, 4H), 7.38 (m, 5H), 7.49 (dd, 1H), 7.85 (d, 1H).

N-{4-[4-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-3-(methoxycarbonyl) phenyl] but-3-ynyl} phenoxycarbonylaminophenoxyformate (compound 116)

To a stirred solution of **115** (320.0 mg, 0.60 mmol), phenoxycarbonylaminophenoxyformate (198.4 mg, 0.73 mmol) and triphenylphosphine (55.7 mg, 0.21 mmol) in THF (2 mL) at 0° C was added diisopropylazodicarboxylate (78.2 mg, 0.68 mmol). After addition, the reaction was warmed to room temperature and stirred at room temperature for 2 hours. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, 1:1 hexane/ethyl acetate) to give **116** (350 mg, 73.9%): ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 4H), 2.65 (m, 6H), 2.90 (m, 2H), 3.82 (s, 3H), 4.15 (m, 4H), 4.21 (s, 1H), 6.85 (d, 1H), 7.25 (m, 8H), 7.40 (m, 12H), 7.82 (s, 1H).

Methyl 2- (2- {4- [(1R) (4-chlorophenyl) phenylmethyl] piperazinyl} ethoxy) -5- [4-(aminohydroxycarbonyl amino)but-1-ynyl]benzoate (compound 4) and 2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl amino)but-1-ynyl]benzamide (compound 5)

In a screw top vessel was placed a solution of **116** (350 mg, 0.44 mmol) in methanol (20 mL) and cooled to -78°C in a dry ice-acetone bath. To this vessel was added liquid ammonia (3 mL) and sealed. The dry ice-acetone bath was then removed and the reaction was stirred at room temperature for 16 hours. The reaction was cooled again in a dry ice-acetone bath and the pressure released. The vessel was opened and the solvent was evaporated. Compound 4 was separated by flash column chromatography (silica gel, 9:1 CH_2Cl_2/CH_3OH) as a white solid. The mixture of compound 4 and 5 was further purified by flash column chromatography (silica gel, 9:1 CH_2Cl_2/CH_3OH) to give additional compound **4** (total 31 mg) and compound **5** (contain about 5% compound **4**). Compound **5** was further separated from compound **4** by recrystallization using ethyl acetate-hexane as a solvent (35 mg).

Compound **4**: ^1H NMR ($CDCl_3$) δ 2.45 (m, 4H), 2.70 (m, 6H), 2.90 (t, 2H), 3.75 (t, 2H), 3.83 (s, 3H), 4.18 (t, 2H), 4.21 (s, 1H), 5.34 (bs, 2H), 6.85 (d, 1H), 7.25 (m, 4H), 7.37 (m, 5H), 7.43 (dd, 1H), 7.80 (s, 1H).

Compound **5**: ^1H NMR ($CDCl_3$) δ 2.40 (m, 4H), 2.54 (m, 4H), 2.75 (t, 2H), 2.80 (t, 2H), 3.80 (t, 2H), 4.20 (m, 3H), 5.42 (bs, 2H), 5.80 (bs, 1H), 6.87 (d, 1H), 7.25 (m, 4H), 7.36 (m, 5H), 7.45 (dd, 1H), 8.14 (d, 1H), 8.75 (bs, 1H).

2-(2-{4-[(1R)(4-chlorophenyl)phenylmethyl]piperazinyl}ethoxy)-5-[4-(aminohydroxycarbonyl-amino)but-1-ynyl] benzoic acid (compound **6**)

In a small round-bottomed flask was placed compound **4** (30 mg, 0.05 mmol). To this flask was added 1M KOH/CH_3OH (0.30 mL, 0.30 mmol). The reaction was stirred at room temperature for 48 hours and then cooled in an ice bath. 1M HCl/ether (0.30 mL, 0.30 mmol) was added and the mixture was purified by flash column chromatography (silica gel, 9:1 CH_2Cl_2/CH_3OH) to give **6** as a white solid (9 mg, 31.4%): ^1H NMR (CD_3OD) δ 2.56 (m, 4H),

2.66 (t, 2H), 2.96 (m, 4H), 3.10 (t, 2H), 3.68 (t, 2H), 4.32 (t, 2H), 4.34 (s, 1H), 6.98 (d, 1H), 7.20 (d, 1H), 7.30 (m, 4H), 7.44 (m, 6H).

Example 5

CHO-K1 H1R Binding Assay Protocol

This assay is commonly used to measure the ability of a compound to act as a histamine H1 receptor binding ligand. As this assay employs human cloned H1 receptors it can provide a good approximation of what can be expected when a compound is administered to humans.

Details of the assay procedure are as follows. CHO-K1 cells expressing the human cloned H1 receptor are grown to confluence in tissue culture dishes. Cells are harvested using D-PBS buffer (JRH Biosciences), kept at 4°C, centrifuging to pellet cells (4°C, 500g, 10 min). The final cell pellet is homogenized and resuspended using Tris/sucrose buffer (20 mM Tris, 250 mM sucrose, pH 7.4 at 4°C). Aliquots of the membrane preparation are stored at -70 °C.

On the day of assay, the membrane preparation is thawed and centrifuged (TLA100.3 rotor, 4°C, 15 min, 23,000 rpm). The pellet is resuspended in Tris/sucrose buffer initially and then diluted further as necessary using assay buffer A (50 mM Na/KPO_4, 2 mM $MgCl_2$, 0.5% (w/v) BSA, pH 7.5).

For the binding assay, the membrane preparation, test compound and ^{3}H-pyrilamine (2 nM final) in buffer A with 1% (v/v) DMSO final are incubated in a 96-well polypropylene plate for 3 hours at 37°C. Non-specific binding is determined in the presence of 10 µM pyrilamine. A 96-well harvester (Packard) is used to harvest the 96-well plate onto a GF/B filter plate pre-treated with 0.1% (v/v) PEI. The plate is counted in a Packard Topcounter after adding Microscint 20 (Packard) scintillation fluid. The K_i for each compound at the histamine H1 receptor is then calculated from these counts. The results are displayed in Table 1, *infra*.

Example 6

Inhibition of LTB_4 Production in Human Whole Blood

This assay examines the ability of a compound to inhibit leukotriene B_4 production from human blood stimulated with calcium ionophore. As this production of leukotriene B_4 is mediated via the activation of the 5-lipoxygenase enzyme, this assay is predictive of a compound's ability to inhibit the human 5-lipoxygenase enzyme.

The procedure for the assay is as follows. Blood is drawn from normal human volunteers into tubes containing heparin. 1 ml of the heparinized blood is pipetted into a 1.5 ml polypropylene tube. To this sample is added either different concentrations of the test compound (5 µl) dissolved in DMSO or 5 µl of DMSO as a vehicle control. These samples are incubated in a water bath, at 37°C for 15 min. 5 µl of the calcium ionophore A23187 (at a final concentration of 50 µM) is then added to each sample, which is vortexed and placed back in the water bath for 30 min. The samples are then centrifuged at 2500 rpm for 10 min. at 4°C. 50 µl of the supernatant is transferred into pre-cooled Eppendorf tubes containing 950 µl of enzyme immunoassay (EIA) buffer. A commercially available EIA kit (Cayman Chemical Co., Ann Arbor, MI Arbor) is used to subsequently measure the LTB4 production in the samples. The LTB_4 levels produced in the vehicle control sample is then compared to those in which the test compound has been added. From this a percent inhibition of LTB_4 production by each concentration of test compound is calculated and the IC_{50} for inhibition of LTB_4 production for each test compound is determined. The results are displayed in Table 1, *infra*.

Table 1

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
1	24	1515
15	260	1681
17	23	2041
19	40	9767
21	220	5768
22	12	4222
24	130	3626
2	380	267
25	10	2444

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
28	94	2657
30	58	251
31	15	2101
35	8	1473
36	10	287
37	7	253

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
39	4	1714
7	150	650
42	36	412
3	15	254
8	7	263
44	550	142

Cpd #	CHOH1 K_I (nM)	HWB IC_{50} (nM)
5	135	85
4	420	94
6	4	6589
46	120	122
48	35	106
49	2	2742

Example 7

Antihistaminergic Activity In Vivo

Male, Hartley guinea pigs are obtained from Charles River Labs at a body weight of 350 - 400 grams. Inhibition of histamine activity is measured by the method of Konzett and Rössler (*Naonyn-Schmiedebergs Arch. Exp. Path. Pharmakol.* **195,** 71-74 (1940). Anaesthetized guinea pigs are subjected to artificial ventilation. The endotracheal pressure is recorded. Bronchoconstriction is induced by successive intravenous injections of histamine. The test compounds are administered orally in a 1% methocellulose suspension at set timepoints prior to the administration of histamine.

The results (Table 2) show the percent inhibition of histamine-induced bronchoconstriction by selected compounds at multiple time points post oral dosing. 50% inhibition or greater is considered significant.

Table 2

Cpd #	Dose of test cpd	Time (in hours)	% inhibition
1	5mg/kg	3 hrs	56%
2	2 mg/kg	3 hrs	62%
2	2 mg/kg	6 hrs	66%
30	2 mg/kg	3 hrs	66%

Cpd #	Dose of test cpd	Time (in hours)	% inhibition
30	2 mg/kg	6 hrs	73%
36	2 mg/kg	3 hrs	80%
36	2 mg/kg	6 hrs	92%
7	2 mg/kg	3 hrs	86%
7	2 mg/kg	6 hrs	91%
8	2 mg/kg	3 hrs	65%
44	2 mg/kg	3 hrs	81%
44	2 mg/kg	6 hrs	89%

It can be seen from this Table that compounds of the present invention possess good activity with regard to their ability to inhibit histamine-induced bronchoconstriction. Furthermore, several of the compounds administered at a single dose possess antihistaminergic activity of long duration. For example, **7**, at a dose of 2 mg/kg, still inhibits histamine-induced bronchoconstriction by 91% at 6 hours post oral dosing.

These experiments also indicate that the compounds tested are orally bioavailable.

Example 8

5-Lipoxygenase Inhibitory Activity in vivo

Male, Hartley guinea pigs are obtained from Charles River Labs at a body weight of 350 - 400 grams. Compounds are prepared at a volume of [1-2 mg/ml] in 1% methocellulose for oral dosing. Animals are separated into groups of five (5). Each assay includes a control group dosed with vehicle. Each group of animals is dosed with either vehicle or compound by oral gavage. Animals are allowed to rest for one, three, or six hours after dosing. Control animals are allowed to rest for three hours. At the appropriate times, the animals are

anesthetized with Urethane at 1.5 g/kg, ip. Blood is drawn into a heparinized syringe via cardiac puncture.

Blood (0.5 ml) is aliquoted into separately-labeled 1.5 ml eppendorf tubes. Each sample is loaded with 5 µl of [15 mM] Arachidonic Acid, and placed in a 37 °C water bath for five minutes. After five minutes, the blood is stimulated with 5 µl of [5 mM] A23187 (Calcium Ionophore) and retained in the water bath for an additional 30 minutes. After the thirty minutes, the blood samples are removed from the water bath and centrifuged at 14,000 rpm for 2 minutes. Plasma is salvaged to EIA buffer and an EIA is performed following manufacturer instructions (Cayman Chemical Co., Ann Arbor, MI Arbor).

The results (Table 3) show the percent inhibition of 5-lipoxygenase by selected compounds at multiple time points post oral dosing. 50% inhibition or greater is considered significant.

Table 3

Cpd #	Dose	Time in hours	% inhibition
1	2 mg/kg	1 hour	62%
2	2 mg/kg	6 hours	80%
30	2mg/kg	1 hour	70%
30	2mg/kg	6 hours	94%
36	2 mg/kg	1 hour	80%
7	2 mg/kg	1 hour	88%
8	2 mg/kg	1 hour	88%

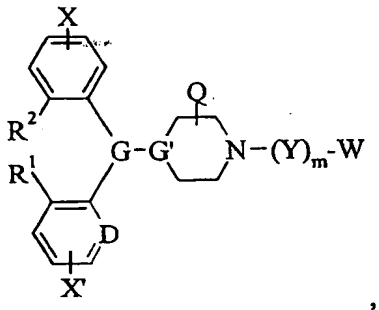
It can be seen from this Table that compounds of the present invention possess good activity with regard to their ability to inhibit the 5-lipoxygenase enzyme. Furthermore, several of the compounds administered at a single dose possess 5-lipoxygenase inhibitory

activity of long duration. For example, **30** at a dose of 2 mg/kg, still inhibits 5-lipoxygenase activity by 94% at 6 hours post oral dosing.

These experiments also indicate that the compounds tested are orally bioavailable.

We Claim:

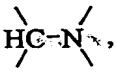
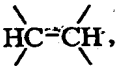
1. A compound of formula I′:



I′

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof, wherein:

X and X′ independently are -H, halo, alkyl, alkenyl, alkynyl, alkoxy, or trifluoromethyl;

G and G′ together form  ,  , or  ;

D is =CH= or =N-;

R^1 and R^2 independently are hydrogen or together are $-(CH_2)_n-$ in which n is equal to 0, 1, 2, or 3;

m is 0 or 1;

Y is $-L^1-$ or $-L^2-V(Z)_t-L^3-$ in which t is 0 or 1;

L^1 is alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q)-, or $-N(R^3)-$;

L^2 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, $-S(O)_2-$, -N(Q′)-, or $-N(R^4)-$, or (b) $-L^4-C(O)-N(Q')-$ or $-L^4(Q')-$, or (c) a direct bond;

L^3 is (a) alkylene, alkenylene, alkynylene, or one of the foregoing in which one or more methylenes are replaced by -O-, -S-, -S(O)-, -$S(O)_2$-, -N(Q′′)-, or -$N(R^5)$-, or (b) a direct bond;

L^4 is alkylene;

V is (a) a divalent arene, a divalent heteroarene, or a divalent saturated heterocycle when t is 0, or (b) a trivalent arene or trivalent heteroarene when t is 1;

Q, Q′, and Q′′ independently are hydrogen, -$AC(O)OR^6$, or -$AC(O)NR^6R^7$;

W is -$N(OM)C(O)N(R^8)R^9$, -$N(R^8)C(O)N(OM)R^9$, -$N(OM)C(O)R^8$, -$C(O)N(OM)R^8$;

Z is -$N(OM')C(O)N(R^{10})R^{11}$, -$N(R^{10})C(O)N(OM')R^{11}$, -$N(OM')C(O)R^{10}$, -$A'C(O)N(OM')R^{10}$, -$A'C(O)NR^{10}R^{11}$, or –$A'C(O)OR^{10}$;

A and A′ independently are a direct bond, alkylene, alkenylene, alkynylene, yloalkylaryl, yloarylalkyl, or diyloalkylarene or one of the foregoing in which one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -$S(O)_2$- and/or one or more methylidenes are replaced by =N-;

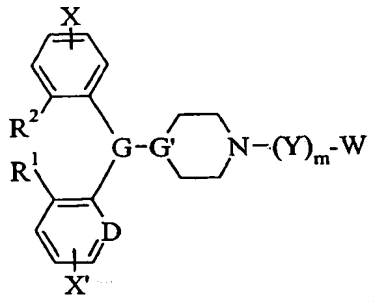
M and M′ independently are hydrogen, a pharmaceutically acceptable cation, or a metabolically cleavable group; and

R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, and R^{11} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkylaryl, alkylarylalkyl, or one of the foregoing in which one or more methylenes are replaced by -O-, -NH-, -S-, -S(O)-, or -$S(O)_2$- and/or one or more methylidenes are replaced by =N-;

provided that, other than the oxygens bound to the sulfurs in -S(O)- and -$S(O)_2$-, when one or more methylenes are replaced with -O-, -NH-, -S-, -S(O)-, or -$S(O)_2$- and when one or more methylidenes are placed with =N-, such replacement does not result in two heteroatoms being covalently bound to each other;

and further provided that when m is 0, W is -$C(O)N(OM)R^8$, -$C(O)NR^8R^9$, or –$C(O)OR^8$.

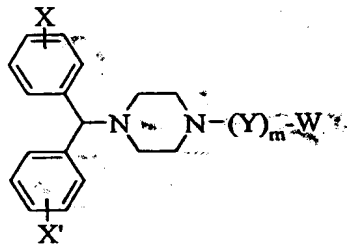
2. The compound of claim 1 having the formula I'':



I''

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

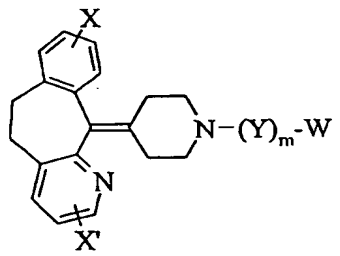
3. The compound according to claim 1 having the formula II:



II

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

4. The compound according to claim 1 having the formula III:



III

and the geometrical isomers, enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

5. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 0 and W is $-C(O)N(OH)-R^3$.

6. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1 and W is $-N(OH)C(O)NH_2$.

7. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^1-$, wherein L^1 is alkynylene, yloalkoxy, or yloalkoxyalkyl.

8. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V-L^3-$, t is 0, V is 1,4-phenylene or 1,3-phenylene, L^2 is yloalkoxy, and L^3 is alkylene, alkenylene, or alkynylene.

9. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V-L^3-$, t is 0, V is 2,5-furylene, L^2 is alkylene, and L^3 is alkylene, alkenylene, or alkynylene.

10. The compound according to either of claims 3 or 4 wherein X is -Cl, X′ is hydrogen, m is 1, Y is $-L^2-V(Z)_t-L^3-$, t is 1, L^2 is yloalkoxy, V is trivalent heteroarene, Z is $-AC(O)NR^3R^4$ or $-AC(O)OR^3$, and W is $-N(OH)C(O)NH_2$.

11. A compound selected from the group consisting of compounds **2, 4, 5, 6,** and **30.**

12. A compound selected from the group consisting of compounds **1, 7, 8, 36,** and **44.**

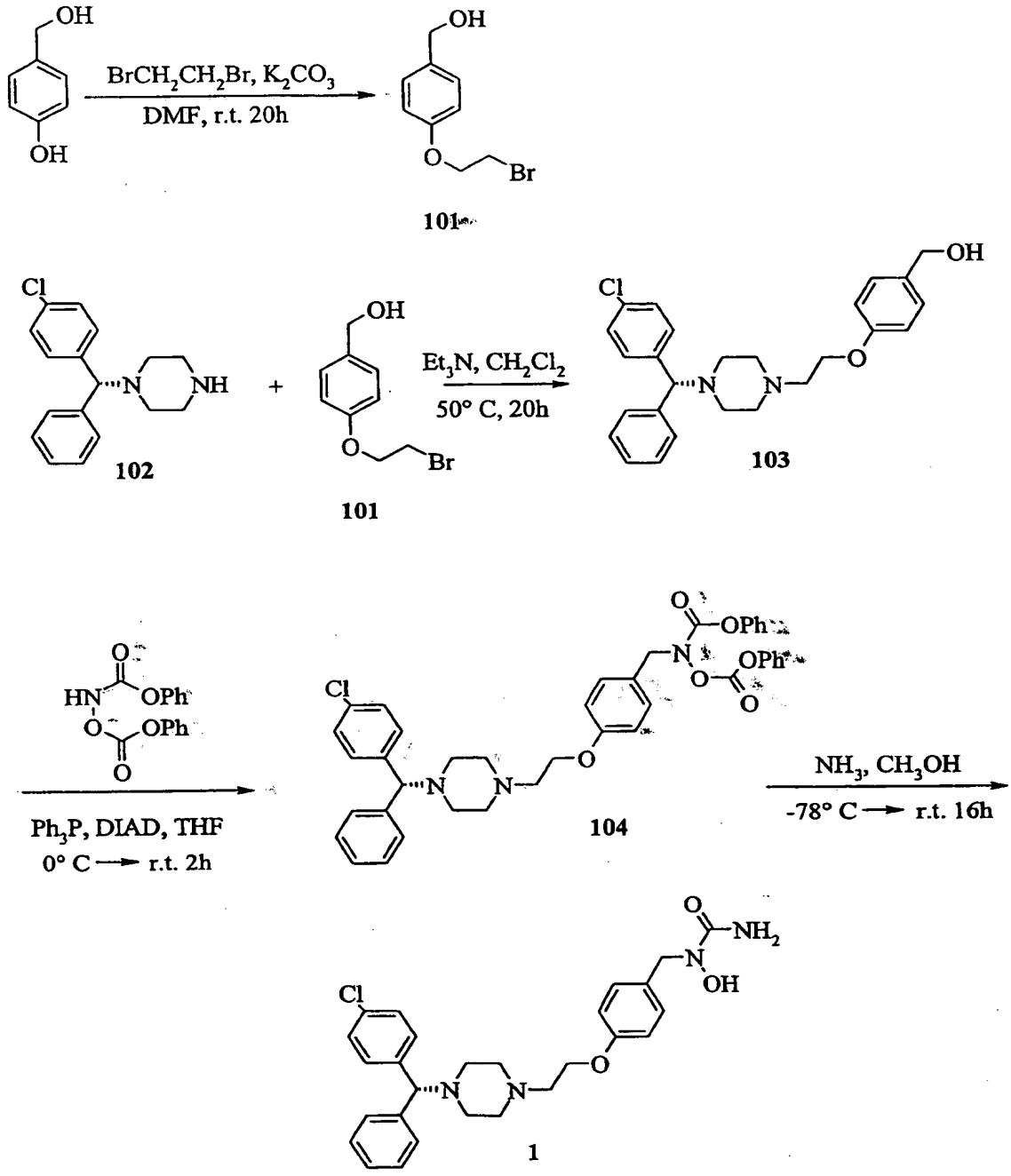
13. A composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims 1-12.

14. A method of simultaneously inhibiting both leukotriene- and histamine- mediated biological processes, the method comprising administering an effective leukotriene- and histamine- inhibiting amount of a compound according to any one of claims 1-12 to a subject in need of such inhibition.

15. A method of treating asthma, the method comprising administering to a patient suffering from asthma an amount of a compound according to any one of claims 1-12 sufficient to reduce or eliminate the asthma.

ABSTRACT OF THE DISCLOSURE

The present invention provides 1,4 substituted piperazines, 1,4 substituted piperidines, and 1-substituted,4-alkylidenyl piperidines compounds. The compounds of the invention are dual function inhibitors having both leukotriene inhibition properties as well as antihistaminergic properties. The compounds are useful for treating asthma and rhinitis. Also provided are methods of inhibiting asthma and rhinitis by administering an effective asthma and rhinitis-relieving amount of the compounds to a subject in need thereof.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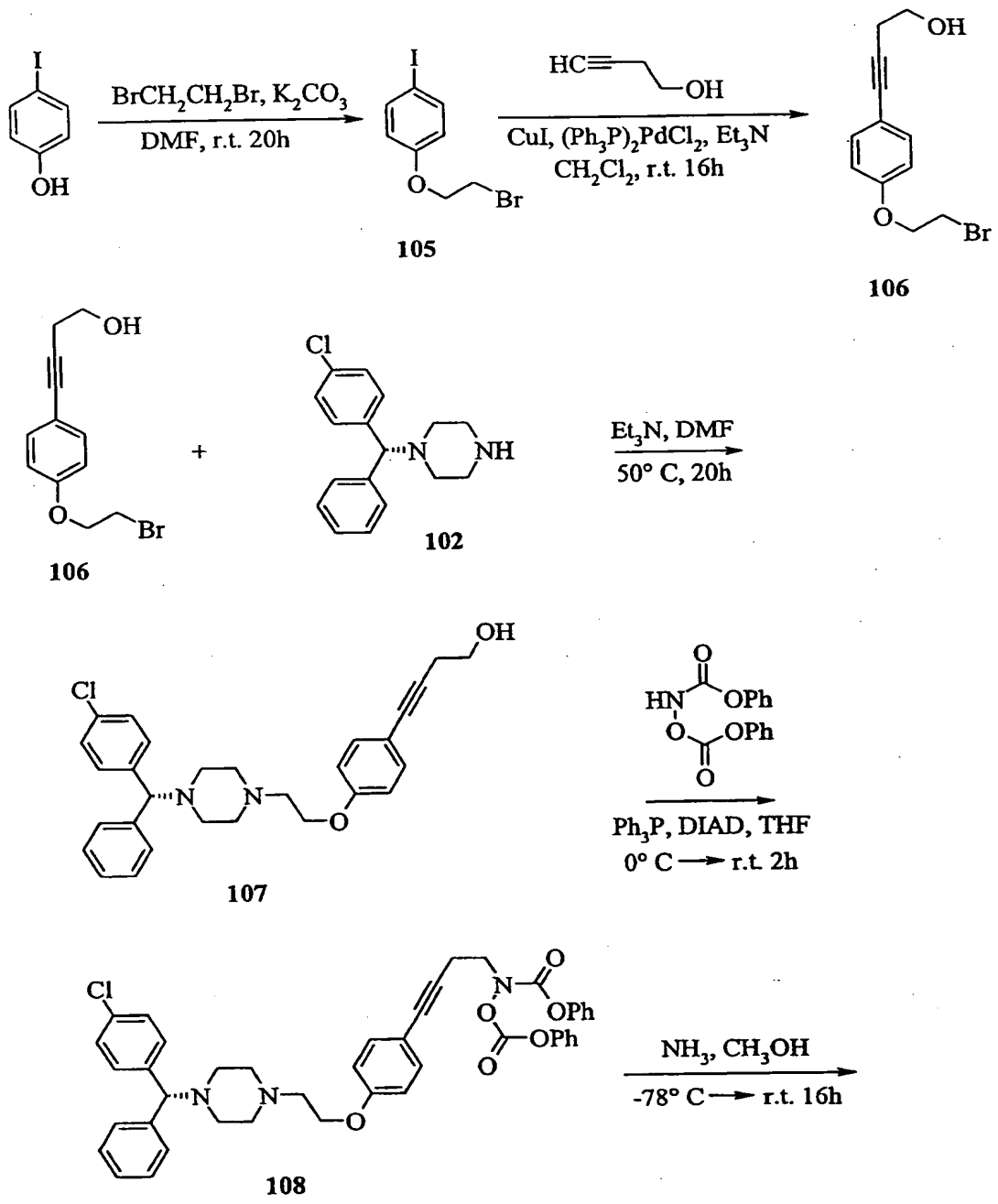
Br
101
Cl
N
NH
102
+
OH
O
Br
101
Et3N, CH2Cl2
50° C, 20h
Cl
OH
N
N
O
103
HN
O
OPh
O
OPh
O
Ph3P, DIAD, THF
0° C → r.t. 2h
O
OPh
N
OPh
O
O
Cl
N
N
O
104
NH3, CH3OH
-78° C → r.t. 16h
O
NH2
N
OH
Cl
N
N
O
1

Fig. 1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DMF, r.t. 20h
HC≡C—OH
CuI, (Ph3P)2PdCl2, Et3N
CH2Cl2, r.t. 16h
105
106
Et3N, DMF
50° C, 20h
102
106
107
Ph3P, DIAD, THF
0° C → r.t. 2h
NH3, CH3OH
-78° C → r.t. 16h
108

Fig. 2

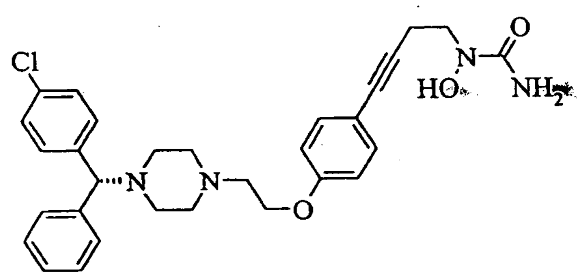

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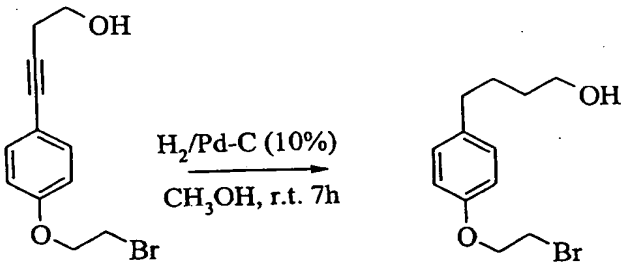
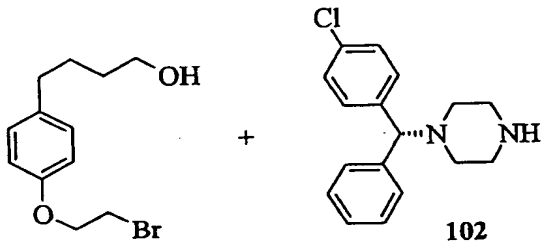
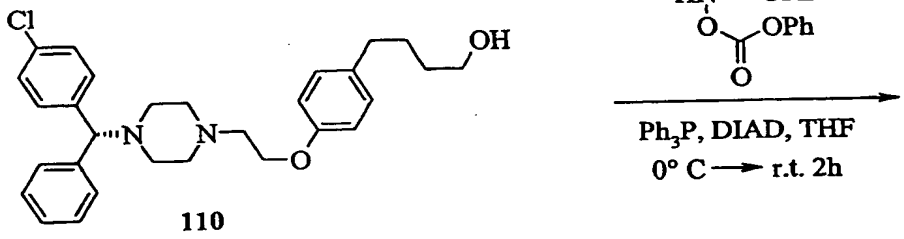
Fig. 2 (cont.)



106 109



109 102



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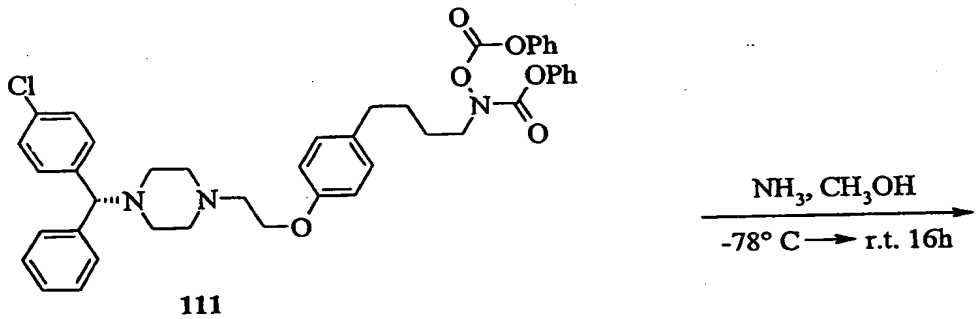

111

Fig. 3

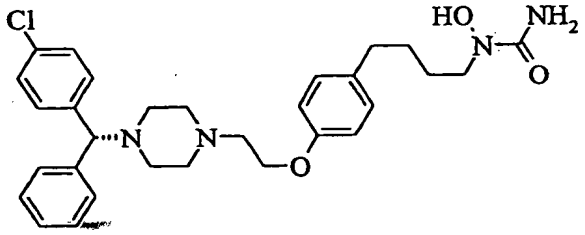

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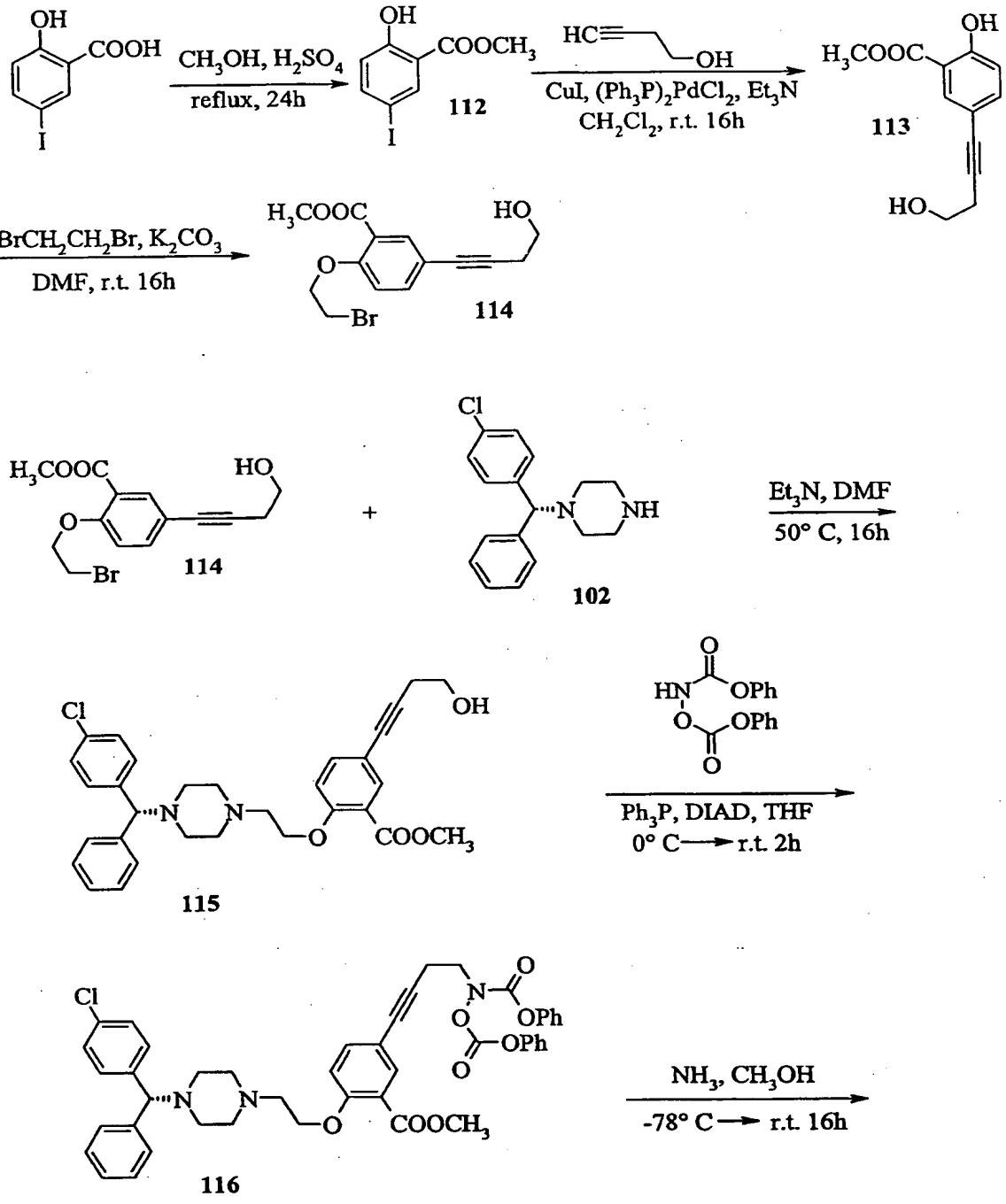
Fig. 3 (cont.)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COOH
I
CH3OH, H2SO4
reflux, 24h
COOCH3
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HC≡
OH
CuI, (Ph3P)2PdCl2, Et3N
CH2Cl2, r.t. 16h
H3COOC
113
BrCH2CH2Br, K2CO3
DMF, r.t. 16h
HO
Br
114
Cl
N
NH
102
Et3N, DMF
50° C, 16h
115
O
HN
OPh
Ph3P, DIAD, THF
0° C → r.t. 2h
116
NH3, CH3OH
-78° C → r.t. 16h

Fig. 4

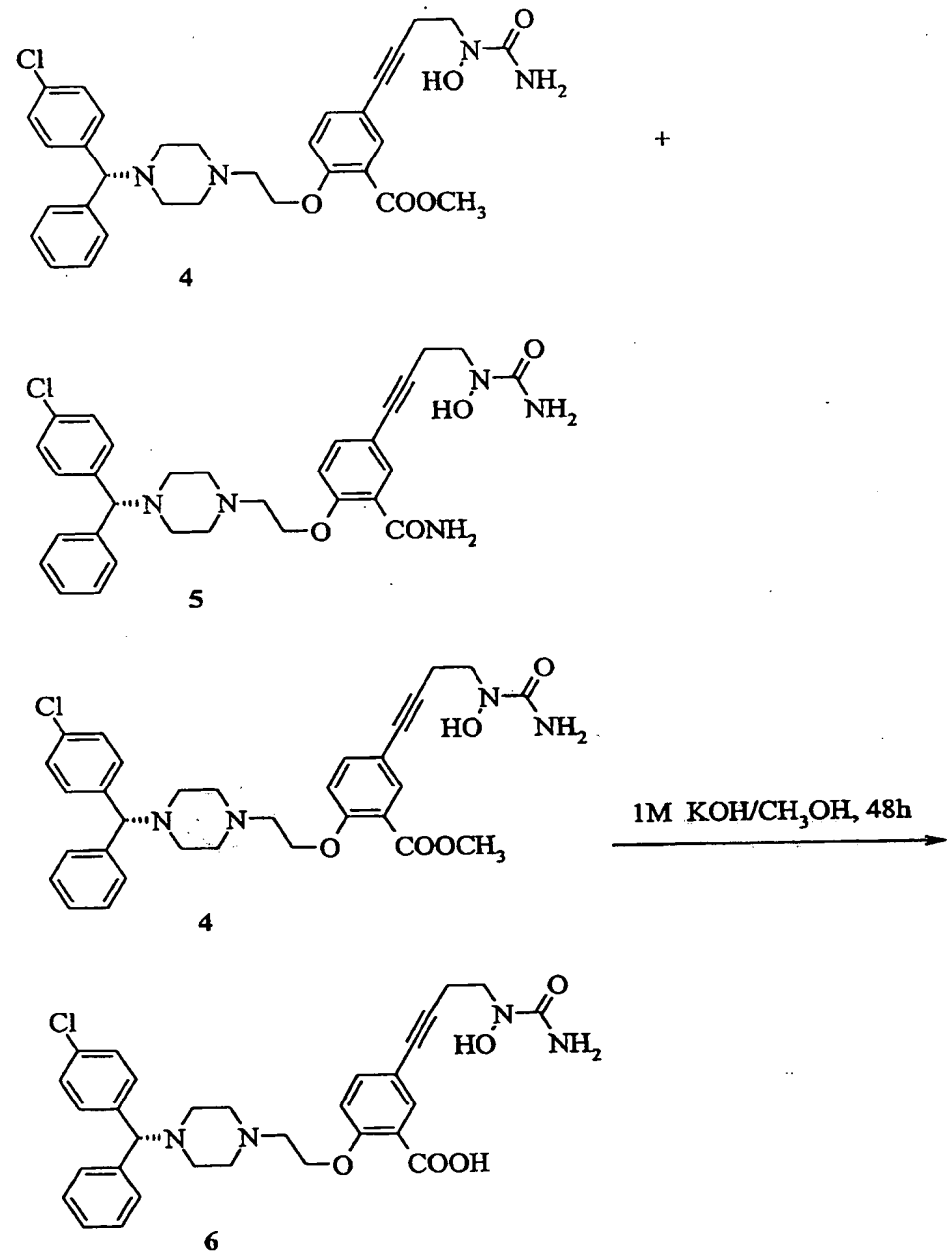
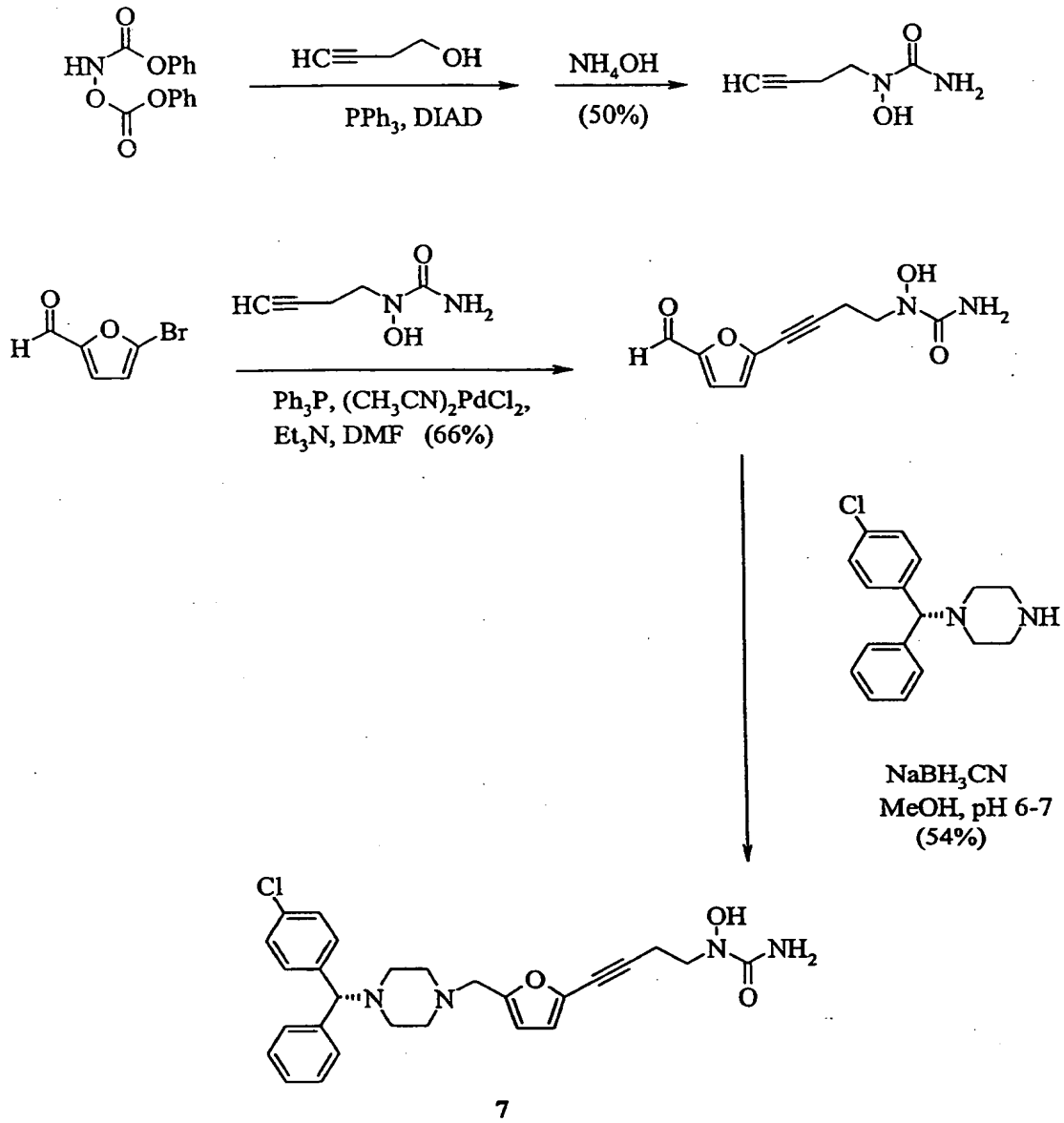


Fig. 4 (cont.)


PPh3, DIAD
(50%)
Ph3P, (CH3CN)2PdCl2,
Et3N, DMF (66%)
NaBH3CN
MeOH, pH 6-7
(54%)

7

Fig. 5

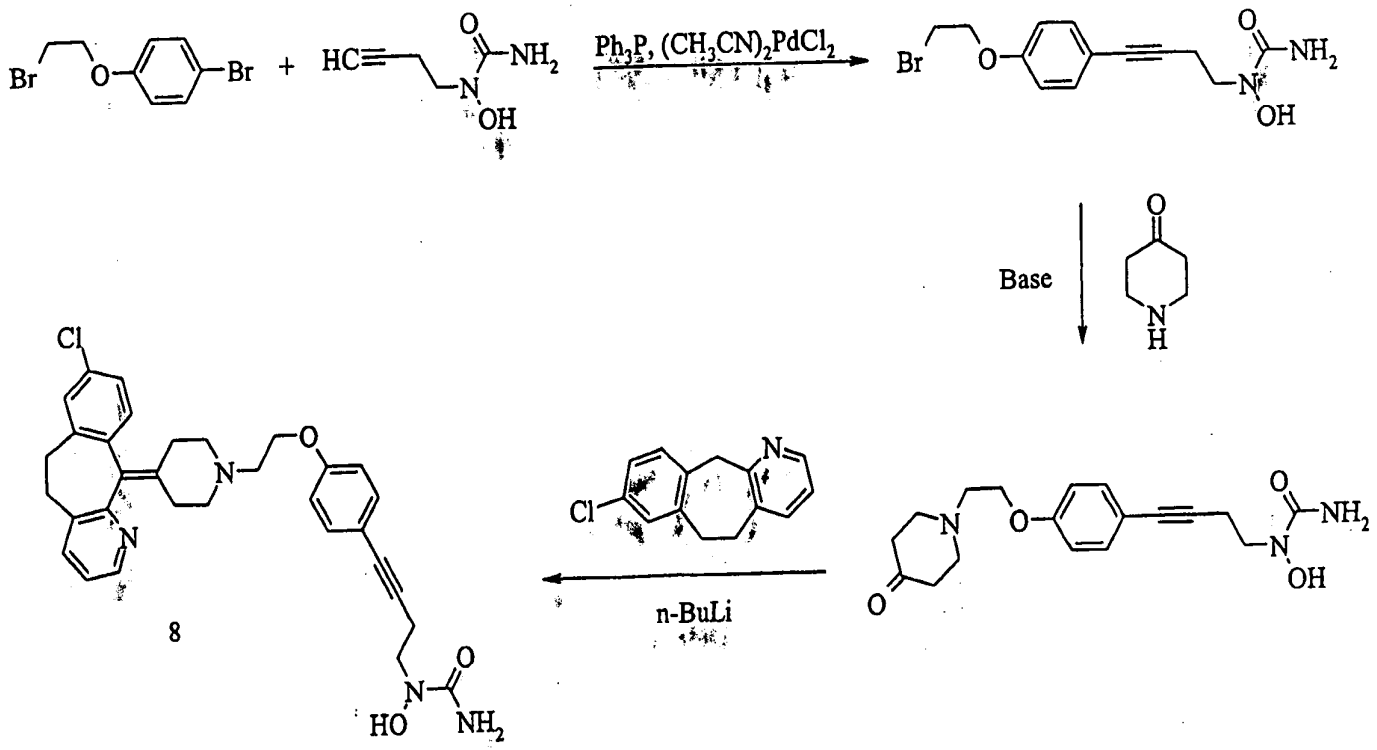

Br
O
Br
+
HC≡
O
NH2
N
OH
Ph3P, (CH3CN)2PdCl2
Br
O
O
NH2
N
OH
Base
O
N
H
Cl
N
O
N
8
HO
N
O
NH2
Cl
N
n-BuLi
O
N
O
O
NH2
N
OH

Fig. 6

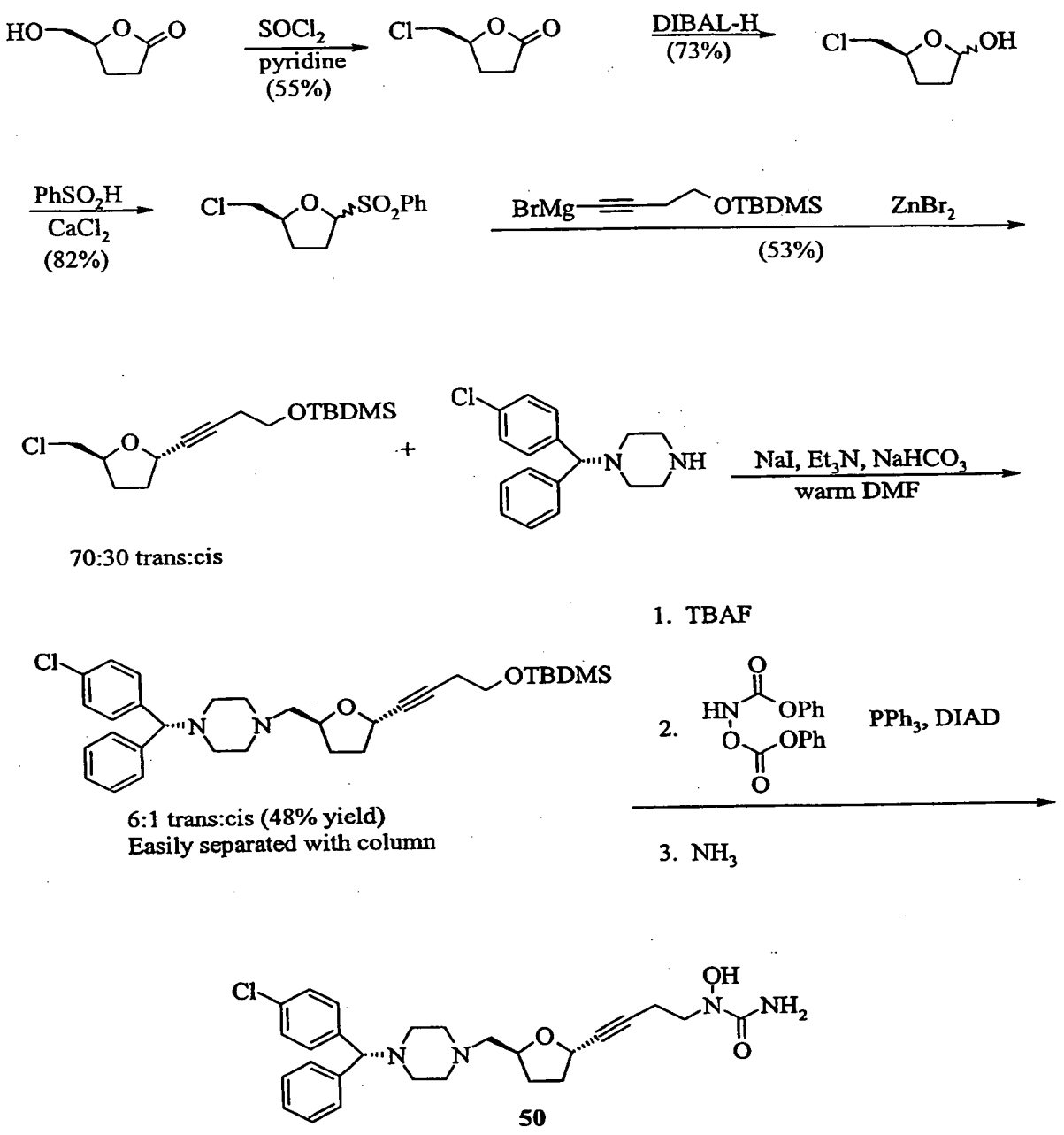

HO
O
O
SOCl2
pyridine
(55%)
Cl
O
O
DIBAL-H
(73%)
Cl
O
OH
PhSO2H
CaCl2
(82%)
Cl
O
SO2Ph
BrMg
OTBDMS
ZnBr2
(53%)
OTBDMS
Cl
O
+
Cl
N
NH
NaI, Et3N, NaHCO3
warm DMF
70:30 trans:cis
1. TBAF
Cl
OTBDMS
N
N
O
2.
HN
OPh
O
OPh
O
PPh3, DIAD
6:1 trans:cis (48% yield)
Easily separated with column
3. NH3
Cl
OH
N
NH2
O
N
N
O
50

Fig. 7